Melatonin in Critically Ill Children

Jennifer Ruth Foster^{1,2,3,4}

¹Department of Paediatrics, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada

²Department of Pediatrics, Western University, Ontario, Canada

³Children's Health Research Institute, London, Ontario, Canada

⁴Lawson Health Research Institute, London, Ontario, Canada

Address for correspondence Jennifer R. Foster, MD, FRCPC, Pediatric Critical Care, 4th floor link, IWK Health Centre, 5850/5980 University Avenue, Halifax, Nova Scotia, B3K 6R8, Canada (e-mail: Jennifer.foster@iwk.nshealth.ca).

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Abstract

Keywords

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Melatonin, while best known for its chronobiologic functions, has multiple effects that may be relevant in critical illness. It has been used for circadian rhythm maintenance, analgesia, and sedation, and has antihypertensive, anti-inflammatory, antioxidant, antiapoptotic, and antiexcitatory effects. This review examines melatonin physiology in health, the current state of knowledge regarding endogenous melatonin production in pediatric critical illness, and the potential uses of exogenous melatonin in this population, including relevant information from basic sciences and other fields of medicine. Pineal melatonin production and secretion appears to be altered in critical illness, though understanding in pediatric critical illness is in early stages, with only 102 children reported in the current literature. Exogenous melatonin may be used for circadian rhythm disturbances and, within the critically ill population, holds promise for diseases involving oxidant stress. There are no studies of exogenous melatonin administration to critically ill children beyond the neonatal period.

Introduction

Melatonin is an endogenously produced indolamine, best known for its chronobiologic effects on sleep and biorhythms through diurnal secretion by the pineal gland. Melatonin is produced by many tissues in the body and participates in diverse physiologic functions, the extent of which is incompletely understood. Thus, abnormalities of melatonin production that may occur during critical illness have the potential for far-reaching consequences. Circadian rhythmicity may be disturbed in critically ill patients, and supplemental melatonin holds promise for this indication. Additionally, exogenous melatonin may be administered to achieve therapeutic effects at supraphysiologic concentrations. This may have relevance to critically ill populations through antiexcitatory properties, immunomodulation, and a wide range of anti-inflammatory and antioxidant actions. This paper reviews the current understanding of melatonin physiology in pediatrics, including the production, metabolism, and function of the endogenous hormone during

illness. We then explore the roles of exogenous melatonin for critically ill pediatric patients.

Melatonin Physiology

Production

Melatonin, or *N*-acetyl-5-methoxytryptamine, is produced by almost all major taxa of organisms.^{1,2} It is a product of tryptophan metabolism, via serotonin acetylation and methylation. In the mammalian pineal gland, melatonin production is responsive to changes in lighting³ with the rate-limiting step, serotonin acetylation by *N*-acetyltransferase (NAT), being under control of the suprachiasmatic nucleus (SCN). Loss of light is sensed by the retina which transmits a signal to the SCN (the major circadian pacemaker of the central nervous system). This results in norepinephrine release, which acts via both β - and α_1 -adrenergic receptors to upregulate cyclic adenosine monophosphate (cAMP) production. This mediates NAT activity, resulting in greater

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melatonin production. Melatonin binds to MT₁ and MT₂ (Gi protein-coupled membrane receptors with highest receptor density in areas of circadian relevance, such as the SCN)^{4,5} providing negative feedback to the SCN, and melatonin production slows. Light then suppresses norepinephrine release and induces NAT proteolysis.⁶ The resulting decrease in melatonin halts the negative feedback⁷ to gene transcription and triggers a new melatonin production cycle. Thus, melatonin affects the phase and amplitude of circadian oscillations,⁸ and allows pacemakers to adjust to environmental cues.

Pineal melatonin is not stored but is secreted by simple diffusion into the blood and cerebrospinal fluid,⁹ and thus plasma concentrations reflect synthesis and concentrations in the pineal gland.¹⁰ Plasma and salivary melatonin concentrations are also correlated in children.¹¹ In mammals, production by extrapineal tissues such as mononuclear leukocytes, pancreatic islet cells, and the gastrointestinal tract, among others, is well-documented. However, while extrapineal sites contain much higher concentrations of melatonin than the pineal gland,¹² they do not appear to contribute significantly to circulating plasma concentrations. In addition, the dynamics of the fluctuating serum melatonin concentrations cannot be applied to other organs and tissues, where production may not follow a circadian rhythm.¹³ Thus, measurement of circulating melatonin concentrations provides only a limited view of melatonin production within the body.

Melatonin production generally begins around 21:00, peaks between 01:00 and 04:00, and returns to baseline in the morning between 06:00 and 09:00.^{14,15} Circulating melatonin has a physiologic half-life in the range of 20 to 30 minutes.^{16,17} It is metabolized by the hepatic P₄₅₀ enzyme CYP1A2 followed by conjugation to 6-sulfatoxymelatonin (aMT6s), the primary urinary metabolite. Tissue melatonin is predominantly broken down by other pathways.

Melatonin is produced in the fetus, but serum concentrations have been shown to decrease with gestational age,¹⁸ which may be related to both decreased production and increased clearance.¹⁹ There is speculation of a relationship between the increased susceptibility to oxidative stress experienced by neonates and their relatively low melatonin concentrations.²⁰ Serum melatonin concentrations rise shortly after birth, and a distinct circadian rhythm develops between 4 and 12 weeks postpartum.^{21–23} This circadian rhythm demonstrates significant interindividual variability but high intraindividual stability.^{15,24,25} Daily, total pineal secretion and total urinary excretion of aMT6s appear to remain stable throughout most of childhood.^{25–28} However, nocturnal serum melatonin concentration peaks between ages 1 and 3 years and then steadily decreases with increasing patient plasma volume.^{29,30} Age-stratified normal values for both serum^{29–31} and salivary^{21,32} melatonin concentrations and urinary aMT6s excretion^{21,23,26,32,33} have been reported. Melatonin production by nonpineal tissues has not been quantified to date and changes experienced during critical illness have not as yet been explored. However, given the relative mass of nonpineal melatonin and its functional

pleiotropy, it is possible that alterations in production may indeed bear significance to the pathophysiology of critical illness although this remains speculative at this stage.

Actions

Melatonin is known to have broad ranging effects that extend well beyond its chronobiologic functions. Although these roles are incompletely understood,⁷ several may be relevant to the critically ill population. Melatonin is important for both sleep initiation and maintenance³⁴ and contributes to sleep regulation through maintenance of the circadian rhythm³⁵ and neuronal antiexcitatory effects.³⁶ Children with complete suppression of pineal melatonin production following craniopharyngioma resection often demonstrate inappropriate sleep-wake cycles.^{37,38} Endogenous melatonin is also involved in vasomotor control and generally acts as a mild antihypertensive agent.³⁹

Animal studies suggest that melatonin may exert complex anti-inflammatory, antioxidant, and antiapoptotic effects.^{40,41} Melatonin is formed by and stimulates several immunologically active cells, including mast cells, monocytes, T cells, natural killer cells,⁴⁰ and epithelial cells.⁴² Melatonin also promotes the release of several cytokines including interleukin (IL)-1, 2, 6, 10, and 12, and interferon- γ .⁷ Melatonin demonstrates pro-oxidant effects by stimulating interferon- γ ⁴³ and activating monocytes.⁴⁴ These effects tend to be protective and have been credited with melatonin's antimicrobial properties.⁴⁵ Melatonin's broad antioxidant actions have been demonstrated experimentally using supraphysiologic concentrations but are unproven at physiologic concentrations.⁷ Melatonin provides mitochondrial protection⁴⁶ and may indirectly prevent apoptosis.⁴⁷ It may also be neuroprotective; pinealectomized animals demonstrate worse neurodegeneration after experimental stroke,⁴⁸ an effect attributed to lack of ischemia/reperfusion injury attenuation. However, the relationship between serum melatonin concentration, that is, pineal melatonin, and nonchronobiologic functions is not known.

Measurement of Melatonin

Measurement of serum melatonin concentrations in children is problematic due to interindividual variation, which may change with age,^{22,29} fluctuating concentrations making single samples insufficient for production estimates,⁴⁹ and significant blood volumes required. Urinary sampling of aMT6s may provide a more readily acceptable alternative⁵⁰ though it may be affected by metabolic processes which are often deranged in critically ill children. Salivary melatonin correlates with serum melatonin in cooperative pediatric outpatients,^{32,51} but its role in critically ill patients remains unclear.

Melatonin Secretion in Pediatric Critical Illness

Pineal function and diurnal variation of melatonin secretion may be affected by several factors common to pediatric

intensive care unit (PICU) admissions, including stress-induced endogenous catecholamines, exogenous adrenergic agents,⁵² opioids,^{53,54} benzodiazepines,⁵⁵ other anticonvulsants,^{56,57} corticosteroids, and a lack of normal lighting cues.⁵² Studies of melatonin secretion in critically ill adults have demonstrated disturbed diurnal rhythms with loss of periodicity in the context of mechanical ventilation,^{50,52} analgesia and sedative administration,⁵⁸ traumatic brain injury,⁵⁸ sepsis,⁵⁹ intensive care unit (ICU) delirium and psychosis,⁶⁰ and thermal injury.⁶¹ Total daily melatonin excretion and serum concentrations have been inconsistently abnormal.⁶² While children may be subjected to similar pathologic processes as their adult counterparts, pediatric physiology and critical illness outcomes often differ and it cannot be assumed that the response of the pineal gland in critical illness is the same in adults and children.

Three studies of melatonin secretion in critically ill children have been reported. The first, a prospective cohort study, assessed 03:00 serum nocturnal melatonin concentrations (NMC) and 12 hourly aMT6s excretion over 5 days in 23 septic and 13 nonseptic patients⁶³ and found that the mean peak NMC in both groups was generally lower than literature references for normal children.^{29,30} Subgroup analysis revealed increased NMC in patients with septic shock and hepatic dysfunction and decreased aMT6s excretion in those with hepatic dysfunction compared with those without. The authors suggested that increased serum melatonin in septic patients may be secondary to both increased melatonin production and decreased hepatic metabolism, and recommended evaluation of both urine and serum for melatonin status in critically ill children.

The same group expanded upon this work with a study of 20 septic and 20 nonseptic PICU patients over 10 days.⁶⁴ They found no significant difference in NMC or 24-hour aMT6s excretion between study groups with mechanical ventilation, with benzodiazepine and opioid sedation, or in comparison to literature references. In septic patients, shock and nonsurvival were associated with higher NMC while aMT6s was lower in the nonsurvivors and in septic patients with liver dysfunction. Again, the authors suggested that nonsurvivors and those with hepatic dysfunction had lower serum melatonin metabolism, possibly related to CYP1A2 mRNA suppression by increased proinflammatory cytokines.⁶⁴

A final study reported repeated serum melatonin concentrations during a 14-hour period starting from 22:00 on day 2 after intubation for 16 deeply sedated, mechanically ventilated, prepubertal children in the general PICU.⁶⁵ Peak NMC was higher than age-stratified literature controls in 14/16 patients. All patients demonstrated abnormal melatonin rhythmicity, and 2/16 had absence of peak NMC. Normal PICU lighting was associated with lower serum melatonin levels compared with darkness, though not compared with literature controls. There was no statistically significant relationship between serum melatonin concentrations and inotropes, sedative agents, or Pediatric Risk of Mortality (PRISM) score.

The data on melatonin concentrations and pineal function in the heterogeneous milieu of pediatric critical illness are incomplete. Many questions remain, including the feasibility

of using salivary melatonin or urinary aMT6s as surrogates for blood sampling and the effect of the PICU environment itself on melatonin secretion. Melatonin concentrations, actions, function, and receptor density in the peripheral tissues during critical illness, as well as the effects of altered melatonin secretion remain unexplored. Well-designed trials exploring this area are needed.

Melatonin Administration in Critical Illness

Melatonin has been prescribed to children for multiple indications.⁶⁶ It is usually used as a sleep aid, demonstrating reasonable efficacy in sleep problems.⁶⁷ While this capitalizes on melatonin's known chronobiologic functions and is intuitive to investigate in populations with abnormal serum levels such as the critically ill, the pleiotropy of the molecule suggests that melatonin administration may result in additional effects. This section focuses on potential uses of exogenous melatonin in the PICU and supportive data from general pediatric, neonatal, surgical, adult, anesthesia, and basic science literature. Several melatonin agonists are being tested or marketed including TIK-301, agomelatine, tasimelteon, and ramelteon. As they have not been adequately studied in children, the discussion focuses on melatonin itself.

Pharmacokinetics

Melatonin may be administered enterally or intravenously (IV). Fast-release oral preparations are rapidly absorbed and demonstrate first-pass metabolism through the liver with a half-life ($t_{1/2}$) in the range of 40 minutes and bioavailability of 1 to 37%.⁶⁸ In nine critically ill adults given oral melatonin, maximum serum concentration occurred at 0.5 hours and $t_{1/2}$ was 1.47 hours.⁶⁹ In children from 6 years of age onward, IV melatonin shows a $t_{1/2}$ in the range of 40 minutes.⁷⁰ In premature infants, the $t_{1/2}$ is 17 to 21 hours, likely as a result of lower CYP1A2 concentrations. Pharmacokinetics in infants and toddlers are not known. The effects of critical illness on the pharmacokinetics of melatonin administration in children, enteral or IV, are unexplored.

Sleep and Maintenance of Circadian Rhythm

Patients in the PICU experience poor sleep quality, lower sleep efficiency, decreased sleep continuity, and loss of day-night differentiation.^{52,71} Importantly, sedation is not the same as sleep and, in fact, analgesic/sedative agents decrease rapid eye movement (REM) sleep that is the restorative component of sleep.^{72,73} Melatonin has the potential to improve several sleep characteristics: quantity through its effect on sleep latency; quality through sedative-sparing effects as it does not decrease slow-wave or REM sleep⁷⁴; and day-night differentiation through its effects on the intrinsic pacemakers and particularly the SCN.

Several studies of nocturnal melatonin administration in children, predominantly those with intellectual disabilities, have demonstrated decreased sleep latency, increased total sleep time, and improved sleep continuity.⁷⁵⁻⁷⁷ Melatonin did not improve sleep in seven non-ICU adult males with sleep disturbance following severe traumatic brain injury.⁷⁸

However, healthy patients in either a simulated ICU environment⁷⁹ or with forced dyssynchrony resulting in abnormal circadian rhythm⁷⁴ experienced modest benefits in overall sleep efficiency.

Experience in Pediatric Critical Care

Melatonin is prescribed in some PICUs for sleep, sedation, and to reestablish circadian rhythmicity (personal communications), though the practice has not been formally described. A detailed search of the literature revealed no studies of exogenous melatonin administration, for any indication, to critically ill children beyond the neonatal period. This is an area that warrants further investigation of both existing practice and outcomes.

One research group has performed several randomized, placebo-controlled trials examining the antioxidant effects of melatonin in neonates, a patient group at high risk of oxidative injury.⁸⁰ No study was reported to have been blinded, and most studies involved repeated melatonin doses of 10 mg/kg. These are the only studies identified in a group of critically ill patients within the pediatric age range.

Experience in Adult Critical Care

There have been four trials of the effect of exogenous melatonin on sleep and circadian rhythm in critically ill adults. In eight adults with respiratory illness in the ICU, 3 mg melatonin for 2 nights improved sleep quality and quantity as measured by actigraphy. As this was not a crossover study design, the authors postulated that it was possible that the homeostatic sleep drive was high (as a result of sleep deprivation) at the point when melatonin was given.⁸¹ In a double-blinded trial of 3 mg of oral melatonin nightly in 32 tracheotomized ICU patients, there was no appreciable effect on nurse-observed sleep compared with placebo, though daytime sleep was not evaluated.⁸² In 24 mechanically ventilated adult ICU patients, sleep was more efficient and included longer periods of REM phase with nightly melatonin, though patients did not report better sleep. In this study, the melatonin group had slightly worse sleep-disturbing characteristics (older age, delirium) at a baseline.⁸³ Finally, 82 critically ill, mechanically ventilated patients with differences in the study populations at baseline had decreased requirements for other nocturnal sedation (hydralazine) in those randomized to nocturnal, enteral melatonin.⁸⁴ Overall, the existing literature on melatonin for sleep in critical illness is limited by small patient numbers, single-center studies, lack of standardized electroencephalogram (EEG) evaluation of 24-hour sleep, and nonuniformity about concomitant use of other sedatives. A proposed trial by Huang and colleagues may address several of these issues.⁸⁵

Role in Disease States

In humans, melatonin shows promise in conditions in which oxidative stress plays a role in disease pathophysiology such as sepsis, stroke, postcardiopulmonary bypass, and trauma. Along with its physiologic anti-inflammatory properties, melatonin administration that achieves supraphysiologic

concentrations effectively scavenges and reduces reactive oxygen species^{86,87} prevents lipid peroxidation,⁸⁸ decreases mitochondrial hydroperoxide levels, restores and maintains glutathione cycling,⁶⁵ inhibits gene expression of pro-oxidant enzymes,⁴⁷ and downregulates proinflammatory cytokines and chemokines⁸⁹ in animal models.

In 20 neonates with asphyxia who received eight enteral doses of study drug, melatonin was associated with decreased markers of lipid peroxidation and nitric oxide (NO) production compared with placebo, though not compared with healthy controls.⁹⁰ In studies of both surgical neonates⁹¹ and premature infants (< 32 weeks gestation age) with grade III or IV respiratory distress syndrome who received 10 IV doses of study drug,^{92–94} melatonin reduced nitrite/nitrate levels (a marker for NO synthesis) and other markers of inflammation, and showed a trend to improved clinical outcomes.

Sepsis

Murine models of sepsis have been used repeatedly to demonstrate melatonin's anti-inflammatory properties: decreases inflammatory mediators such as IL-1 β and tumor necrosis factor- α ; increases anti-inflammatory mediators like IL-10 and the activities of anti-inflammatory enzymes; decreases neutrophil infiltration to tissues; decreases lipid peroxidation and improved plasma antioxidant capacity; decreases plasma NO and downregulates inducible and neuronal nitric oxide synthase; favors energy efficiency and adenosine triphosphate (ATP) production; and attenuates apoptotic cell death.^{95–99} Clinically, melatonin results in increased response to adrenergic agents and decreased hypotension, decreased organ dysfunction, and improved survival.^{95,96} In vitro, exogenous melatonin demonstrates antimicrobial actions that decrease intracellular infection with bacteria.^{100–102} Melatonin decreases mortality from viral infection in mice¹⁰³ and has been proposed as a viable therapy for Ebola virus infection.¹⁰⁴

Septic patients demonstrate alteration of sleep-wake cycles, augmentation of oxidative and nitrosative stress, and a significant inflammatory reaction, all of which may be ameliorated with melatonin. A study of 20 septic newborns who received two oral doses of study drug (melatonin 10 mg/kg or placebo) within 12 hours of diagnosis demonstrated a significant reduction in lipid peroxidation products and a trend toward improved clinical outcomes with melatonin administration.¹⁰⁵ Other than this initial small neonatal study, pediatric data are absent. Phase 1 trials for melatonin use in sepsis have begun, with a focus on adult populations.¹⁰⁶

Myocardial Ischemia Including Post-cardiopulmonary Bypass

Melatonin may prove protective or therapeutic for any condition with a pathophysiologic basis in ischemia and reperfusion through minimization of inflammation, decreased oxygen radical damage, and attenuated apoptosis. In vitro, melatonin attenuates human red blood cell oxidative injury from cardiopulmonary bypass (CPB).¹⁰⁷ In rat models,

melatonin for global myocardial ischemia results in decreased apoptosis and improved hemodynamics,¹⁰⁸ while intraoperative melatonin protects against renal¹⁰⁹ and hepatic¹¹⁰ injury from CPB. In humans, adults undergoing CPB who had higher physiologic melatonin levels, from time of day effects, showed lower postoperative inflammatory mediators and lactate dehydrogenase.¹¹¹ Melatonin therapy in the congenital heart population has the potential to attenuate postoperative low cardiac output syndrome.

Burns

Melatonin may benefit burn patients through stimulation of the oxidative defense system and immune system, analgesia, and maintenance of circadian rhythm.¹¹² In vitro, melatonin attenuates microvascular hyperpermeability¹¹³ and in murine models diminishes organ injury¹¹⁴ and coagulopathy¹¹⁵ induced by burns. Further work in humans is needed.

Traumatic Brain Injury and Stroke

Melatonin use for patients with both stroke and traumatic brain injury warrants evaluation. Murine models of melatonin for brain edema demonstrate decreased edema, infarct area, and blood-brain barrier permeability.¹¹⁶ Melatonin for closed-head injury decreased contusion volume and significantly increased rate of recovery.^{117,118}

Potential Therapeutic Indications in PICU

Delirium Prevention

Although the pathogenesis of delirium is not fully understood, circadian rhythm abnormalities, sleep disturbances, and melatonin production abnormalities may play important roles.^{60,119,120} Experimentally, low postoperative melatonin levels are correlated with delirium in the ICU.¹²¹ Enteral melatonin has been found effective in preventing delirium in elderly patients admitted to a general medical service¹²² and for preventing and managing delirium in elderly surgical patients.¹²³ In children, preoperative melatonin decreased emergence delirium in a dose-dependent manner when compared with midazolam.¹²⁴ There is a growing awareness of the significance of delirium in the PICU,¹²⁵ but experimental trials are lacking.

Sedation

Melatonin induces sleep and provides anxiolysis,^{126,127} which may occur via GABAergic system activation.¹²⁸ Thus, for children it appears mainly effective in minimally stimulating procedures such as auditory brainstem response testing,¹²⁹ sleep EEG,¹³⁰ and steal induction preoperatively.¹³¹ In 105 children, preoperative melatonin was as effective as midazolam in decreasing anxiety and decreasing postoperative sleep disturbances.¹³² However, melatonin did not improve sedation characteristics in children undergoing magnetic resonance imaging¹³³ or dental procedures.¹³⁴

While it is unlikely that melatonin will be adequate as a single agent for sedation in the context of the PICU, it holds promise as an adjunct or sedative-sparing agent. In adults, preoperative melatonin decreased the ED₅₀ for propofol and

thiopental for loss of response to verbal command and eyelash reflex,¹³⁵ decreased the dose of propofol required to obtain deep sedation (bispectral index 45) and intubation by 20 mg,¹³⁶ and improved pain, sleep, and sedation postoperatively.¹³⁷ Melatonin is being studied as part of enteral sedation regimens in adult ICUs,¹³⁸ holds promise as a benzodiazepine-sparing agent, and warrants examination in the pediatric population.

Analgesia

Experimentally, melatonin demonstrates dose-dependent analgesic effects.¹³⁹ The proposed mechanisms are mainly derived from animal data and include decreased anxiety,^{128,140} increased β -endorphins,^{128,141} enhanced antinociception,^{142–144} and involvement of various receptors in the brain and spinal cord.^{145,146} In human placebo-controlled trials, melatonin preoperatively reduced postoperative opioid requirements.^{128,140} A study of 60 neonates up to 32 weeks gestational age who underwent intubation for mechanical ventilation compared standard induction agents with standard plus 10 mg/kg IV melatonin. The authors reported lower pain scores after paralysis wore off with melatonin, which also decreased pro- and anti-inflammatory cytokines (IL-6, 8, 10, 12) leading the authors to postulate modulation of pain mediation through anti-inflammatory effects.¹⁴⁷

These studies suggest the possibility of using melatonin as an adjunct or opioid-sparing agent in the PICU, where levels of pain with ongoing intubation and ventilation may not be high, yet patients are frequently uncomfortable.

Hypertension

Arterial blood pressure demonstrates diurnal variation, with higher daytime pressures. Humans without a nocturnal nadir have a higher risk of cardiovascular disease and demonstrate lower nocturnal melatonin.¹⁴⁸ Exogenous melatonin tends to reduce nocturnal blood pressure preferentially in those with, or at risk of, hypertension.^{149,150}

Seizures

Status epilepticus is a frequent admission diagnosis in pediatric critical care, and several critically ill patient groups have lower seizure thresholds. Melatonin facilitates GABA transmission, resulting in antiepileptogenic properties and possible anticonvulsant activity.¹⁵¹ Although an attractive theoretical option for seizure control, evidence for its efficacy is weak at best.^{152,153} Melatonin may decrease nocturnal seizures in children but most importantly does not aggravate seizures in children with epilepsy.¹⁵⁴ This latter property may render melatonin a useful sedative or analgesic adjunct in patients with a lower seizure threshold.

Safety

Melatonin use in children and adolescents is generally considered off label.^{155,156} Safety has not been identified as an issue in human investigations of exogenous melatonin administration, including those with high single doses,¹⁵⁷ high cumulative doses over several weeks¹⁵⁸ or months,¹⁵⁹ or

during the study of infants and children,^{76,160} including premature infants and neonates.¹⁶¹ One author has called for full disclosure of animal data to families prior to prescribing melatonin,¹⁵⁶ as nonhuman studies have indicated a significant effect of melatonin on reproductive physiology. However, large studies with long (up to 5 years) follow-up have found no adverse effects, and particularly no alterations in puberty.^{76,160,162} The long-term safety profile, specifically the safety profile in critical illness, has not been systematically evaluated and is warranted.

Conclusion

"Melatonin in critically ill children" describes a field about which little is known. Knowledge of melatonin production during pediatric critical illness is in its infancy. Initial investigations into pineal function and serum melatonin concentrations may assist in guiding therapy for chronobiologic dysfunction, but results show heterogeneity and do not provide information on melatonin production and function within nonpineal tissues during critical illness. The promise held by exogenous melatonin administration for a variety of indications during critical illness is largely unexplored, particularly in the pediatric population. Early researchers will need to be guided by basic science and adult data, as well as studies from other areas of medicine.

Conflict of Interest

Dr. Foster holds research grants from Lawson Health Research Institute and Children's Health Research Institute for the study of melatonin secretion in pediatric critical illness.

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