

Melatonin Supplementation in Undetermined Pediatric Deaths

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Losing Sleep in North Carolina over Pediatric Exogenous Postmortem Melatonin.

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Abstract

Since 2015, the North Carolina Office of the Chief Medical Examiner has investigated seven deaths of infants and toddlers, aged 2 months to 3 years, with exogenous melatonin detected upon toxicological analysis. Melatonin concentrations ranged from 3 to 1,400 ng/mL in postmortem whole blood. While the cause and the manner of all seven deaths were classified as undetermined, the analytical findings are noteworthy. Melatonin is generally considered a safe, natural product appearing in many over-the-counter supplements geared toward young children to facilitate calmness and improve sleep. Melatonin is a neurohormone, which regulates not only circadian rhythms and natural sleep but also other physiological functions. Endogenous melatonin production, derived from essential amino acid metabolism, does not begin until pineal gland maturation at ~3 months of age with concentrations in plasma peaking during periods of darkness at ~0.2 ng/mL. Administering commercially available melatonin supplements to infants results in levels substantially greater than endogenous sources, which should not be assumed to be safe just because of their endogenous nature. The finding of exogenous concentrations in some postmortem pediatric cases warrants attention. Several topics of interest surrounding these postmortem melatonin findings will be considered, such as minimal regulatory control over commercial products as well as the potential impact on hazardous sleeping conditions. This manuscript will outline the physiological effects of melatonin and detail the case studies from the North Carolina medical examiner system. Forensic toxicology laboratories should consider including melatonin at exogenous concentrations in their testing schemes for appropriate postmortem infant and toddler cases.

Introduction

Melatonin, or *N*-acetyl-5-methoxytryptamine, is structurally related to tryptophan (Trp) and serotonin. It is an indole neurohormone produced and secreted by the human pineal gland and plays a role in the regulation of circadian rhythm, immune function and influencing the sleep/wake cycle (1). Recognized for its sleep-inducing, anti-oxidative, anti-inflammatory, anti-aging, anti-cancer, anti-coagulopathic and neuroprotective effects, endogenous melatonin concentrations peak around late childhood and decrease with age (2–5). Certain neurodevelopmental and neurodegenerative disorders are associated with a decreased endogenous concentration of melatonin circulating in the body compared to age-matched controls. The European Medicines Agency granted melatonin a temporary recommendation for use in France for children with autism spectrum disorder (6). Pediatric insomnia experts outside the USA suggest a role for prescription melatonin for children with delayed sleep phase syndrome (7, 8).

In the USA, melatonin is sold over-the-counter (OTC) as a dietary supplement because it occurs naturally in some foods (9). Heavily marketed in the media in 1995, melatonin was cited as “the all-natural nightcap” (10). Melatonin supplementation first gained interest in the forensic

toxicology community because of its potential use in the aviation industry to treat jet-lag effects in pilots (9). During the last few years, partially attributed to daily disruptions from the coronavirus disease 2019 (COVID-19) pandemic, sales of melatonin, advertised as a cheap and easy way to improve sleep, increased at a rapid rate (11, 12).

While doses marketed for healthy sleep cycles originally ranged from 1–10 mg in oral pill form for adults, high-dose preparations up to 60 mg per capsule are now available. Studies have shown that an 80-mg single oral dose ($n = 20$) in adult males resulted in a peak serum average of 33 ng/mL, 1.3 h post-dose (13). A 100-mg single oral dose ($n = 5$) resulted in a peak serum average of 101 ng/mL, 1.0 h post-dose (14). The elimination half-life in adults is ~40 min (7, 14), suggesting that after a 2-mg oral dose, serum melatonin levels return to the basal level within 4 h. Within 1 h of ingestion of 1–5 mg, melatonin concentrations are 10–100 times higher than an adult’s physiological nocturnal peak (~0.09 ng/mL) and return to basal levels within 4–8 h (3, 15). Generally, peripheral blood melatonin concentrations are influenced by the gastrointestinal tract via the hepatic portal vein (16). Oral melatonin is subject to first-pass metabolism impacting its bioavailability. It is metabolized by liver cytochrome P450

enzymes, mainly CYP1A2, to 6-hydroxymelatonin and subsequently conjugated to its main urinary excretion product of 6-sulfatoxymelatonin (3).

Since melatonin is not regulated by the U.S. Food and Drug Administration (FDA) as an approved therapeutic agent (17), there is no standard dose, and minimal certification of quality is needed for commercial preparations (9). Labels that include a third-party certification, such as Consumer Lab, NSF International, UL, and US Pharmacopeia, have been suggested as the safest preparations, but it is not required. This form of quality control is merely a verification of ingredients and evaluation for select contaminants, not a thorough assessment. Interestingly, polls show that the American public overwhelmingly assumes that the FDA reviews the safety and effectiveness of dietary supplements before they are marketed (18). Rather, the Dietary Supplement Health and Education Act of 1994 deems the manufacturer responsible for ensuring the safety of its own products, with the FDA being able to remove concerning agents only after multiple adverse event reports and, sometimes, further studies. Countries outside the USA regulate melatonin more strictly with limited applications for prescription use (19).

Increased marketing efforts to promote OTC melatonin to parents of children offer orally disintegrating supplements or liquid with fruit flavors or chocolate. Some products go as far as suggesting improved subjective feelings of bliss, happiness, peace and/or calm on the label. Melatonin supplements specifically advertised toward children suggest a dosage between 0.05 and 3 mg before sleep (19). Over the last few years, the target age for melatonin supplements has been lowered by some manufacturers to include children as young as 24 months, while internet product reviews document caregivers providing it to even younger children.

Melatonin has been proven to be relatively non-toxic with side effects such as dizziness, headache and nausea and is considered a “minimally toxic” compound when taken in excess (20). Furthermore, most instances of accidental overdoses in children do not require treatment (21). There were 53,521 single exposures to melatonin reported to the American Association of Poison Control Centers in 2020, with 81.9% in children aged ≤ 5 years old; this was an increase of 67% in that age group from 2019; and outcomes were nearly universally benign, but most were not followed up (22).

Despite the growing popularity, guidelines are sparse for consumers and health-care providers regarding use for children without a neurodevelopmental need (7, 23). The American Academy of Pediatrics (AAP) encourages consultation of a pediatrician before administering melatonin supplements. They also suggest shopping for a third-party verified product and recommend starting with the lowest dose (24). General public awareness of melatonin is important as there have been instances where supplements were provided to children in a day-care environment, unbeknownst to the parents, resulting in extensive investigations and criminal charges (21).

Case Identification

Details of the sleeping environment are essential in distinguishing between sudden infant death syndrome (SIDS), accidental suffocation and other causes (25). Much variability currently exists among medical examiners and coroners across the USA in the classification of unexpected infant deaths (25). The Centers for Disease Control and Prevention (CDC)

defines a more general term of sudden unexpected infant death (SUID) as the “sudden and unexpected death of a baby less than 1 year old in which the cause was not obvious before investigation” (26). The USA was one of a few countries that experienced a diagnostic shift in unexplained infant deaths with a decline in SIDS and an increase in deaths attributed to other causes such as accidental suffocation (27). North Carolina’s medical examiner system adopts the definition that SIDS remains a diagnosis of exclusion (28) and does not currently utilize the overarching term of SUID, meaning that SIDS is classified as a natural manner of death. Instead, these cases are distinguished by manner: undetermined, natural (SIDS) and accident-related fatalities.

In 2015, the North Carolina Office of the Chief Medical Examiner (NC OCME) laboratory first became aware of exogenous melatonin in a pediatric case. To date, there have been a total of seven pediatric cases classified as toddler or younger, where melatonin was detected at concentrations consistent with exogenous administration. Two additional cases were identified where melatonin was specifically mentioned as being provided to the toddlers during the pediatric death investigation but was not detected upon toxicological analysis. The case series outlined will assist the forensic community by strengthening the limited postmortem pediatric exogenous melatonin data available in the literature (21, 29). Rather than opine about the theoretical negative consequences of melatonin supplementation, any additional topics herein are designed to stimulate discussion around the diverse role of melatonin in the pediatric body.

Between 2015 and 2021, 1,911 children, 0–4 years of age, were accepted into the medical examiner system in North Carolina. Over 90% of those cases had blood or liver homogenate specimens suitable for an organic base screen by the NC OCME Toxicology Laboratory. Seven hundred and sixty-one cases were classified as undetermined manner with unknown means of death. Seven of these undetermined cases (0.92%) were discovered to have melatonin, identified and quantitated by a secondary laboratory, consistent with exogenous supplementation. One-thousand one hundred and fifty cases were classified by means/manner other than unknown/undetermined, including 43 cases classified as SIDS and 128 cases that are pending final certification.

Methods

At the NC OCME, cases are routinely screened for OTC, prescription and illicit drugs using an organic base extraction with gas chromatography–mass spectrometry–nitrogen phosphorus detector (GC–MS–NPD), as described previously (30). Melatonin has been rarely observed in adult postmortem casework because the routine GC–MS–NPD organic base screen performed in our laboratory lacks sensitivity. When present because of exogenous supplementation, melatonin may be identified with a limit of detection (LOD) of ~ 50 ng/mL with a 2-mL blood extraction depending on extraction efficiency, specimen quality and instrument performance. Liver tissues are prepared at a 1:4 dilution in water, and then 2 g of the resulting homogenate are extracted for cases involving children. With an alphaprodine internal standard retention time of ~ 8.8 min on the GC–MS, melatonin elutes at ~ 12.2 min. Alternatively, cases have been sent to a reference laboratory for targeted analysis when details from the death investigation are consistent with melatonin supplementation.

The quantitation of melatonin in blood for all cases was performed by a reference laboratory. The confirmation method, courtesy of the secondary testing laboratory, is available as part of the Supplementary data.

Case Histories

Case 1 (2015)

A 3-month-old female was found unresponsive in a crib with her surviving twin (29). She and her twin were fed formula by their parents before being put to sleep together in the crib. A more detailed summary of this case is reported by Shimomura et al. As per the investigation, the twins were routinely provided 8–10 daily doses of 5 mg melatonin supplements as a sleep aid. It is unclear if the supplementation occurred directly or via the formula. Melatonin administration was not recommended by any medical professional. Furthermore, >20 bottles of OTC melatonin were found at the residence. Analysis revealed a melatonin concentration in postmortem blood of 1,400 ng/mL. Other toxicological findings included the presence of atropine, likely related to resuscitation efforts. The pathologist certified the case as undetermined for both cause and manner of death and documented the uncertainty surrounding the contribution of melatonin to the infant's death.

Case 2 (2019)

A 2-month-old female was found unresponsive, faceup, in her bassinet by her mother at 0730 h. She was last seen by her grandmother late the evening prior to death and was reportedly last fed at 0100 h by her mother. This child was part of a preterm twin birth. The child and her twin were fed by breast and with formula. The night prior to the death, there was a social gathering at the residence. The surviving twin sibling stayed with a caregiver across the street. When questioned, the mother indicated she was taking melatonin, but not giving it directly to the baby. Toxicological analysis found only melatonin at a concentration of 460 ng/mL in blood. The final pathologic diagnosis was an undetermined manner and means of death with a recognition of the presence of elevated melatonin and mild chronic tracheitis. As noted by the pathologist, this level of melatonin is higher than what would be expected in an adult taking an OTC sleep aid and is inconsistent with the explanation that the mother was simultaneously taking the supplement and breastfeeding. The pathologist noted in the autopsy summary that although the effects of such levels are unknown at this age, there is a likelihood of the child being directly administered the supplement.

Case 3 (2017)

A 3-month-old infant was fed 5 oz of formula at 2100 h the night before death. He was found faceup in a bassinette at 0500 h the next morning with “noisy breathing and clear sputum from mouth.” According to recollection from the mother, the infant felt hot, and an axillary temperature of 106°F was obtained. He had been placed to sleep wearing a onesie, sleep blanket and a separate blanket within his sleep space. This infant was transported by his parents to a medical center in cardiac arrest where he died. Toxicology analysis only detected melatonin with a confirmation of 170 ng/mL in aortic blood. The final pathologic diagnosis included details of

a recent fever (with no source of infection identified); pericardial, pleural and thymic petechiae; congenital absence of left kidney (this was known and present in the child's medical history) and resuscitation-related injuries. The cause of death was listed as undetermined with the pathologist noting an elevated melatonin level as an unusual finding in a toxicological workup of an infant, but it was interpreted to be non-toxic and not sufficient to explain the death.

Case 4 (2021)

A 5-month-old infant was found unresponsive on a couch where he had been sleeping with an adult despite inconsistent lividity patterns in comparison with reports on how the infant was found. The infant had tested positive for COVID-19 ~1 month prior to his death. More recently, he had been experiencing diarrhea, vomiting, cough, feeding issues and fussiness for the past 72 h, and, according to his caregiver, he was given a small dose of children's acetaminophen. Investigation revealed two open bottles of melatonin in the mother's purse, yet no report she provided this to the child. Toxicology analysis only detected melatonin with a quantitative confirmation of 82 ng/mL in the postmortem blood. The pathologist classified this death as undetermined and cited sickle cell trait (with sickled erythrocytes identified on microscopic evaluation), recent COVID infection, a hazardous sleep environment with possible asphyxia and the presence of melatonin as a toxicological finding.

Case 5 (2017)

A 3-year-old male was found unresponsive in bed in the morning after a night of illness with vomit near him. His past medical history was significant for possible autism, sleep apnea, FOXP1 (forkhead box P1) gene abnormality, reactive airway disease and remote adenoid surgery. Three months earlier, he was taken to the hospital for “flu-like symptoms.” The child was in the state foster system and moved into this home 10 days prior, sharing a room with other children. He was noted to be hot to the touch the day prior to his death, not eating or taking in fluids, and appeared to be ill. At 2330 h, he was moaning in bed from unspecified discomfort. His caregivers administered acetaminophen and returned him to bed. The report of the medical examiner noted that he typically had multiple daily bowel movements, but there was an absence of them the day leading up to death. The scene investigation did not uncover the source of any melatonin supplementation although the melatonin concentration was determined to be 73 ng/mL in iliac vein blood. Toxicological analysis also detected acetaminophen at a concentration of <10 mg/L. The final pathologic diagnosis mentioned an intraparenchymal hemorrhage (middle lobe of the right lung), serosal adhesions (cecum to the peritoneal wall) and hydrocephalus of the brain. The cause of death was undetermined with a summary note that the significance of exogenous melatonin cannot be determined, while no apparent natural disease process was identified to explain the death.

Case 6 (2019)

A 5-month-old male infant who was in the 25th percentile for weight was found unresponsive while co-sleeping with his father in an unsafe sleep environment, which included loose bedding on a love seat. This infant had been bottle fed early in

the morning and was found deceased ~5 h later. Investigation revealed the grandmother's claim to witnessing the mother crushing melatonin to add to this infant's formula. This infant had recently developed a cough, and the parents provided him with OTC medication for treatment. Found on scene, during the investigation, was a bottle of honey-based cough medicine with added melatonin to promote restful sleep. Toxicology analysis only detected melatonin with a confirmation of 10 ng/mL in iliac vein blood. The final pathologic diagnosis notes an unsafe sleeping arrangement with co-sleeping by the parent and mildly elevated melatonin blood level. The cause of death was undetermined with a pathologist note, indicating that the role of melatonin, at roughly 10× the normal level found in an adult, was unclear.

Case 7 (2015)

A 2-year-old male toddler was found unresponsive, face-down in his crib in the morning. The child had diarrhea a week prior with possible other cold symptoms, but according to family, he was acting normally the day prior to death. Death investigation revealed melatonin bottles in the home and noted that providing melatonin was a routine occurrence. Toxicological analysis detected only melatonin with a concentration of 3.0 ng/mL in the femoral blood. The pathologist classified this death as undetermined with no anatomical findings at autopsy; postmortem viral cultures were positive for rhino/enterovirus, coronavirus and adenovirus.

Results and Discussion

Summary of postmortem findings

Several themes emerged from the identified cases organized in [Table I](#) from the highest to lowest melatonin concentration (ng/mL). In five of the seven cases, the children were under 1 year of age, which is younger than recommended for melatonin supplementation. This time frame also coincides when concerns of unsafe sleeping conditions are emphasized. Infants aged 0–3 months lack, or are still developing, the strength for head and neck control of their bodies, which is a critical skill for removing oneself from a potentially asphyxiating sleep situation ([31](#), [32](#)). In addition to age, two out of these five were not found in a supine position, which is a recommended position by the AAP to help mitigate sleep-related infant deaths. All five infants were also noted to be sleeping in an unsafe location with three specifically noted to be sharing a sleep space and others having crowded or soft items in the sleep space. All these factors pose additional barriers to creating a safe sleep environment.

As noted in [Table I](#), the origin of melatonin was identified during the medical examiner investigation in five of the seven cases. Several parents stated that melatonin was being provided routinely to help with sleep. In one case, melatonin was noted as an added supplement to the child's formula, whereas another case was unclear as the parent stated to be taking melatonin herself while the child was both breast and formula fed. In some cases, direct melatonin supplementation was not explicitly stated; however, a source of melatonin was found either in the home or with the caregiver. In the other two cases, evidence of melatonin bottles was not uncovered during the death investigation despite an elevated melatonin concentration finding upon toxicological analysis. It is unknown in these two cases if information was being withheld

by the parent/caregiver during the death investigation or if there is another explanation for the increased levels of melatonin. Several of these cases were only discovered because of detailed scene investigation revealing melatonin supplementation followed by a targeted approach for detection and confirmation.

Interestingly, only two additional cases of exogenous melatonin were detected in the entire pediatric population in North Carolina during the time of this study. A 14-year-old was found following a suicidal overdose of bupropion where melatonin was qualitatively identified among the toxicological findings. The other case involved an 11-year-old with a concentration of 10 ng/mL melatonin in iliac vein blood after she requested melatonin from her 19-year-old brother to help her sleep. Both 5-mg and 10-mg melatonin tablets were found on scene from supplements he consumed on a regular basis, but it was unclear which dose was provided to the child. The case was certified a natural pediatric death with complications of probable Sudden Unexpected Death in Epilepsy (SUDEP).

Melatonin biosynthesis

An understanding of L-Trp metabolism ([Figure 1](#)) is important when establishing the relationship between melatonin and related compounds in the body. The endogenous metabolic pathway starts with Trp, an essential amino acid obtained from food. Only a small percentage (~5%) of Trp crosses into the pineal gland where it is hydroxylated to 5-hydroxytryptophan (5-HTP), decarboxylated to serotonin (5-HT), acetylated to *N*-acetyl serotonin (NAS) before the final methylation to melatonin ([3](#), [33](#)). The consequences of exogenous melatonin on the central nervous system (CNS) are not entirely understood, but melatonin and NAS readily cross the blood brain barrier ([21](#), [34](#), [35](#)), and there may be some increase in CNS serotonin levels ([36](#)).

Melatonin chemical synthesis

A Canadian study by Erland and Saxena quantified melatonin in 30 commercial supplements ([37](#)). Melatonin content ranged from -83% to +478% of what was listed on the label and lot-to-lot differences varied by as much as 465%. In addition, serotonin contamination was found in 26% of the supplements ([37](#)). Ingestion of manufactured Trp resulted in eosinophilia–myalgia syndrome (EMS), causing illness including death ([38](#)) as evidenced by the 1989 EMS outbreak ([39](#)). The outbreak was attributed to contaminants in Trp. Williamson et al. characterized seven contaminants found in three different preparations of melatonin. It was determined that six of these contaminants were analogues of those found in Trp and closely related to melatonin ([40](#)). In at least two of the NC postmortem cases, the melatonin supplement was determined to be purchased from a discount store with no third-party verification. The extent of product verification efforts, specifically for known and unidentified contaminants, for all products currently on the US market remains unclear.

Melatonin is commercially manufactured in combination with vitamin B6, magnesium and/or other herbal additives. It is also available in an advanced sleep formula in combination with 5-HTP. Studies performed on oral doses of 5-HTP found that gastrointestinal (GI) upset including nausea, vomiting and diarrhea was the most common adverse effect. The side effects were found to be dose-dependent and may be attributed to peripheral conversion of 5-HTP to serotonin,

Table 1. North Carolina Office of the Chief Medical Examiner Pediatric Deaths from 2015–2021 (Undetermined/Unknown Manner/Mean) Including Information Obtained by Medical Examiner Investigation and Melatonin Concentrations in Postmortem Whole Blood (N = 7)

Case	Age/gender	Scene information/source of nutrition (if infant)	Recent sickness reported?	Unsafe sleep/position found	Infant gestation, multiple birth	Reported source of melatonin	Melatonin (ng/mL)
1	3-month-old/F	Found unresponsive in a crib, shared with twin; exclusively formula fed for the past 3 1/2 weeks	No	Co-sleeping with twin Found prone	36 weeks, twin	Provided 5 mg tablets of dis-solvable melatonin before being placed to sleep as routine practice	1,400 (U)
2	2-month-old/M	Found unresponsive in bassinet in the morning hours; fed formula 6 h earlier; typically fed by breast milk and formula	No	Crowded sleep space with extra bedding Found Supine	35 weeks, twin	Mother noted to be taking melatonin, but not providing it to the infant directly	460 (C)
3	3-month-old/M	Found in bassinet in the morning hours with “noisy breathing” and clear sputum from mouth; oral acetaminophen administration unsuccessful; fed 5 oz of formula the evening prior at 2100 h	Fever noted morning of death, axillary temperature of 106°F	Sleeping in onesie, sleep blanket, additional blanket Found supine	38 weeks	Unknown	170 (P)
4	5-month-old/M	Found unresponsive after co-sleeping on couch; increased fussiness due to recent illness; noted to be formula fed	COVID diagnosis 1-month prior; last 3 days: cough, diarrhea, vomiting	Co-sleeping with adult on couch with multiple pillows and a blanket Found supine	35 weeks	Two opened bottles of melatonin in mom’s purse	82 (C)
5	3-year-old/M	Found unresponsive in bed at foster home, with other children in the room after being provided acetaminophen for symptom relief	Possible fever, day prior with little appetite, moaning, “uncomfortable”-unspecified	N/A	31 weeks	Unknown	73 (P), 320 (C)
6	5-month-old/M	Found unresponsive ~5 h after having been fed a formula bottle in the early morning	Recent cough	Co-sleeping with adult on unsafe sleep surface Found on side	Full term	Family member noted seeing melatonin crushed and added to formula, also provided OTC cough medicine with added melatonin	10 (P)
7	2-year-old/M	Found unresponsive in crib in the morning hours	Diarrhea week prior	N/A Found prone	Full term	Given 3 x 3 mg melatonin tablets at night for sleep	3 (P)

Abbreviations: U, unknown; C, central; P, peripheral; N/A, not applicable.

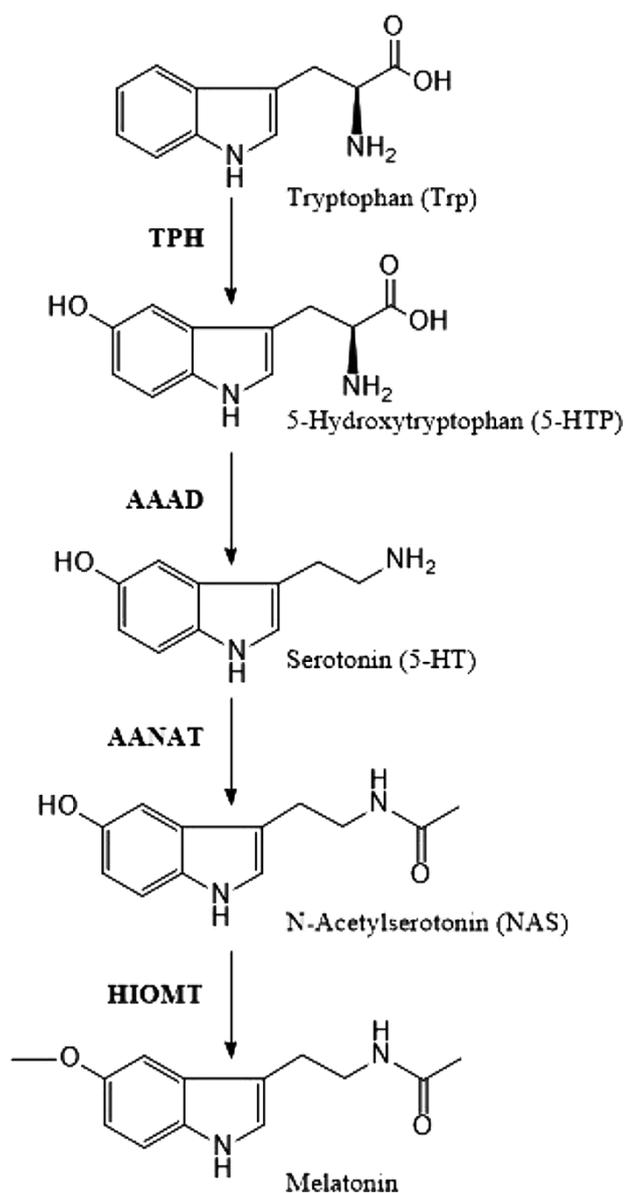


Figure 1. Melatonin synthesis in the pineal gland. TPH (tryptophan hydroxylase); AAAD, also known as AADC (L-aromatic amino acid decarboxylase); AANAT, also known as SNAT (aralkylamine N-acetyltransferase or serotonin N-acetyltransferase); HIOMT, also known as ASMT (hydroxyindole-O-methyltransferase or acetylserotonin-O-methyltransferase).

which increases gut motility (41). Similar symptoms were identified as noted in Table I based on information provided during the death investigation.

Pediatric melatonin

The human pineal gland develops completely postpartum; therefore, a fetus and newborn infant will not synthesize and secrete pineal-derived endogenous melatonin, rather it is mainly supplied directly through placenta and maternal milk, respectively. The pineal gland development, subsequent sleep-wake rhythms, and body temperature rhythm do not exhibit circadian variation in a child until 9–12 weeks of age (3, 42). Abnormalities have been noted in SIDS infants concerning endogenous serotonin and melatonin concentrations in biological fluids (43, 44). Also noteworthy, commercial infant

formulas do not currently contain melatonin among the list of ingredients (35, 45). The concept for addition of melatonin and/or its analogues or precursors to a synthetic night-time formulation has been proposed (46).

Unlike adults, where melatonin has a relatively short half-life of ~40 min, preterm infants have a longer elimination half-life of 17–21 h (4, 23). This slow clearance makes establishing a daily circadian rhythm while using exogenous melatonin problematic in infants (4, 23). Children >3 years old have a melatonin half-life similar to that of an adult. Also concerning is an infant's ability to metabolize xenobiotics. CYP1A2 levels are 20–25% of adult levels in children aged 3–12 months, and slightly older children have ~50% function (23). Considering the reported increase in half-life for infants along with (and caused by) diminished capacity for metabolism, the observations of detectable exogenous melatonin in pediatric cases at the NC OCME versus a lack of detectable exogenous melatonin in the majority of adult cases involving exogenous melatonin, seems plausible.

Lok et al. found that bright-light exposure after melatonin ingestion does not reduce subjective sleepiness but does increase body temperature and proximal skin temperature while decreasing distal skin temperature (47). This suggests that the administration of melatonin to an infant, who also may be exposed to artificial, environmental light sources when awake or feeding shortly after supplementation, may experience variations to their natural temperature control cycle (48). Erden documented a report of a 3-year-old child who experienced hypothermia, abdominal pain and restlessness because of 3-mg daily doses of melatonin for autism (49). None of the NC pediatric cases noted any evidence of hypothermia prior to death; however, Cases 3 and 5 were documented for experiencing fevers around the time of death. It is unclear if the thermoregulatory response was due to an acute illness, directly influenced by either exogenous melatonin or any compounds related to its metabolism and receptor action, which could invoke a hyperthermic response.

Oral melatonin-Trp-vitamin B6 solution, up to 4 mg, was used to sedate newborns undergoing a cerebral magnetic resonance imaging with no reported side effects (50). Notwithstanding the many questions and small number of clinical studies, exogenous melatonin has been cited as being potentially useful in treating some pediatric diseases (46) and improving neurodevelopmental outcomes (51).

Several decedents were either co-sleeping or found in a less than optimal space with either blankets or crowding, as demonstrated in Table I. While melatonin is not classified as a true sedative-hypnotic, it has been reported to cause sleepiness, a soporific effect and sedation (2, 20). Can exogenous melatonin from supplementation play a role in the exacerbation of unsafe sleeping conditions for pediatric cases? It is a complex question and one that warrants additional investigative studies.

Maternal melatonin

At daily peak circadian rhythm, human breast milk will naturally contain ~24 pg/mL melatonin, yet levels will be undetectable during the day (46, 52). At this time, extensive studies do not exist, analyzing breast milk melatonin concentrations after exogenous maternal supplementation, as the practice of taking melatonin is currently discouraged for breastfeeding and pregnant women by the medical community (20). However, general rules of drug distribution into human breast milk

can be applied. Melatonin's short-half-life would render it less likely to accumulate in breast milk (53).

The United States Department of Agriculture (USDA) Drugs and Lactation Database (LactMed) database information on melatonin references ~ 1 ng/mL as the increase in breast milk concentration following oral melatonin use (52). These data raises questions regarding the account of events in Case 2. The mother described taking oral melatonin prior to breastfeeding. Melatonin was found at a concentration of 460 ng/mL in postmortem blood, and this must be interpreted with the consideration that the average 2-month-old child consumes ~ 150 mL per feeding (54). It is relevant to note that the mother initially indicated exclusively formula-based feeding before altering her story to include breastfeeding.

Summary

Some caregivers are currently providing commercially available melatonin supplements to infants and young children to assist with sleep, regardless of the product label's recommended age for use, as evident by these undetermined cases. It is prudent to remind caregivers that non-rhythmical sleep is normal and temporary for an infant during their pineal gland development phase and to consult with a medical provider prior to melatonin use. As a child ages into a natural circadian rhythm, good sleep habits, such as regular bedtime routines, dark and quiet sleeping environments and the avoidance of caffeine in their diet, should help all family members benefit from better sleep patterns (7). Limited studies have been performed on sexual maturation and reproductive cycle impact in growing children who have taken or are currently using melatonin supplements on a regular basis (55, 56). Additional long-term pediatric studies, including a comprehensive endocrine assessment, are necessary to appropriately evaluate its overall safety (20, 23). Melatonin has the potential for clinical applications once it is systematically evaluated with consideration of its hormonal physiological characteristics (57).

The NC OCME laboratory does not currently have the in-house capabilities to determine concentrations of melatonin, melatonin-related compounds or metabolites. Expanding laboratory capabilities to include melatonin and related compounds as part of a comprehensive toxicology panel or a targeted analysis for pediatric cases should be considered. Obtaining more analytical information can be important for future work and interpretation purposes because of the many questions surrounding melatonin synthesis and metabolism in this population.

Conclusions

These cases from the NC OCME system raise awareness regarding the administration of melatonin to toddlers and infants who have died from undetermined/unknown causes. Melatonin is not known to be acutely toxic; however, it causes a multitude of systemic effects by way of mechanisms of action that are not entirely understood, especially in developing infants. More guidance is critical for parents and pediatricians who use melatonin as a routine sleep aid for young children. First responders and death investigators should be aware of melatonin supplement bottles, especially if investigating a pediatric death, whether in a private home or a day-care facility. Postmortem toxicology laboratories should

consider including melatonin in a targeted testing scheme for pediatric cases at exogenous concentrations with a LOD of ~ 1.0 ng/mL. Current instances of exogenous melatonin in pediatric casework could be underestimated due to the lack of sensitivity with GC screening methodologies. Forensic pathologists should contemplate the impact of melatonin on their pediatric casework and notate accordingly in the summary of findings, if detected at exogenous concentrations during toxicological analysis, even if the cause and manner of death remain undetermined.

Supplementary data

Supplementary data is available at *Journal of Analytical Toxicology* online.

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Date availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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