



Sleep and Anesthesia

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Since both anesthesia and sleep depress consciousness, bidirectional relationship between them has been further studied. Earlier findings have shown that they share electroencephalographic features and brain regions that are activated in both state of unconsciousness. Despite these similarities, medication-induced sedation provokes different outcome from natural sleep. Enlisting commonly used analgesic drugs, such as benzodiazepines, intravenous agents, benzodiazepine antagonists, opioids, and other adjuvants, the study is comprised of assorted case studies that are clinically applicable or comparable. Acknowledging potential of analgesic drugs on sleep disorders including sleep deprivation, narcolepsy, circadian rhythm disorder, periodic limb movement disorder, and obstructive sleep apnea, the study underscores the clinical importance of studying both fields, sleep and anesthesia. In conclusion, the aim of this review is explaining the consequences of analgesic agents or sedatives on sleep and sleep disorders.

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Key Words Sleep, Anesthesia, Analgesic drugs, Sedatives, Sleep disorders.

INTRODUCTION

Anesthesia is medication-induced reversible state of unconsciousness. Since the patients lose senses and mobility during general anesthesia, observed condition of operation is analogous to sleep [1,2]. Thus, abundant studies have studied their bidirectional relationship. Previous studies have persistently disclosed that they partially share biological mechanism, especially through gamma-aminobutyric acid (GABA)ergic pathway [3-7]. Common areas both involved in sleep and anesthesia are found to be GABA positive neurons of ventrolateral preoptic and median preoptic nuclei [8-10], albeit collected evidence is insufficient to articulate the entire mechanism of them [11].

Due to these overlapping brain regions that are activated both in sleep and anesthesia, study on potential role of sedatives and analgesic drugs on sleep is inevitable and clinically important. However, relatively few review articles comprehensively discussed the effect of anesthesia on sleep. The present article therefore reviews how sedatives or analgesic drugs influence sleep related parameters. The study is comprised of commonly used drugs, such as benzodiazepines, anesthetic/analgesic agents, and other adjuvants or stabilizers. Additionally, consequences of analgesic drug in sleep-disordered patients are delineated for future safety of anesthetic subjects. Further studied sleep disorders include sleep deprivation, narcolepsy, circadian rhythm disorder, periodic limb movement, and obstructive sleep apnea syndrome (OSAS).

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ANESTHESIA SLEEP: OVERALL DIFFERENCE IN SEDATION

Although anesthesia and sleep are considered very much alike, they demonstrate clear differences in their sedation. During general anesthesia, consciousness, pain, and motor function are lost completely. As the anesthesia deepens, low frequency and high amplitude activity increases (Table 1) [12]. Electroencephalography (EEG) activity spreads symmetrically and reaches wider areas of the brain than that in sleep. Also, muscle atonia and resulting apnea may occur. While anesthesia is categorized into four different phases, nocturnal sleep is largely divided into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. REM sleep occurs at intervals of 90 to 120 minutes, accompanied by rapid eye movement and muscle tone depression. During three stages within NREM sleep, body temperature and pulse reduce simultaneously. Alike anesthesia, low frequency and high amplitude activity increases as sleep deepens, but EEG activity spreads asymmetrically. During nocturnal sleep, subjects preserve muscle tone and normal breathing. EEG differences between anesthesia and sleep are as follows (Table 2).

Despite aforementioned differences, some phases of anesthesia and stages of natural sleep are parallel to one another. For instance, propofol-induced anesthetic state is similar to NREM sleep. Propofol, anesthetic drug, acts on several brain regions

involved in the initiation and maintenance of natural sleep [13]. Likewise, the ‘excitement phase’ of the anesthesia is comparable to REM sleep [3]. This finding has been validated by research conducted by Steriade et al. [1] Specifically, they treated a sedative to brainstem neurons which are responsible for arousal and REM sleep, and observed the reduction in REM sleep. Such comparable biological mechanism underscores the necessity of studying the effect of anesthesia on sleep.

EFFECT OF COMMONLY USED SEDATIVE AND ANALGESIC DRUGS ON SLEEP (Table 3)

Benzodiazepines: Midazolam and Diazepam

Benzodiazepines are analgesic drugs that act through GABA neurotransmitter as natural sleep does. Many of them increase total sleep time and reduce sleep onset latency, while failing to improve the sleep quality [14] and reducing later stage of slow wave sleep (SWS) [15]. Radulovacki et al. [16] purported that benzodiazepine increased only the lighter stage of SWS (SWS1), showing that midazolam-induced anesthesia increased SWS1 by 158%. Meanwhile, diazepam, another benzodiazepine based drug, also increased SWS1 by 255% and reduced SWS latency by 92% [16]. This finding has been probably due to benzodiaze-

Table 1. Comparison of characteristics of anesthesia and sleep onset, maintenance, and offset [12]

	Anesthesia	Sleep
Onset	<ul style="list-style-type: none"> Induced with medication Less notable effect of environmental factors Operated regardless of circadian rhythm or homeostasis 	<ul style="list-style-type: none"> Naturally initiated Notable effect of environmental factors Operated by circadian rhythm
Maintenance	<ul style="list-style-type: none"> Dose dependent depth and duration Less notable effect of environmental factors 	<ul style="list-style-type: none"> Circadian rhythm and daily cycle dependent duration Cycle of multiple stages of sleep Notable effect of environmental factors
Offset	<ul style="list-style-type: none"> Delayed recovery of alertness Alertness dependent on dose and duration Immediate follow-up anesthetization is possible Probable adverse effects 	<ul style="list-style-type: none"> Quick recovery of alertness Alertness dependent on duration and circadian rhythm Immediate follow-up sleep is difficult Sleep disorders may impair sleep quality

Table 2. Anesthesia and sleep: differences in EEG

	Anesthesia	Sleep
Phase 1: Mild anesthesia	<ul style="list-style-type: none"> Increased alpha waves and delta waves Decreased beta waves 	REM <ul style="list-style-type: none"> Saw-tooth waves Rapid eye movement in electrooculogram Muscle tone depression in electromyogram
Phase 2: Vegetative state	<ul style="list-style-type: none"> Increased alpha waves and delta waves in anterior lead Decreased beta waves 	Stage 1: NREM <ul style="list-style-type: none"> Increased theta waves
Phase 3: Deep anesthesia	<ul style="list-style-type: none"> Burst suppression Alternation between flattening alpha waves and delta waves 	Stage 2: NREM <ul style="list-style-type: none"> Sleep spindles K complexes
Phase 4: Deepest anesthesia	<ul style="list-style-type: none"> Nearly brain death Completely lost EEG 	Stage 3–4: NREM <ul style="list-style-type: none"> Delta wave (Slow wave)

REM: rapid eye movement, NREM: non-rapid eye movement, EEG: electroencephalography.

pine-induced disturbance during sleep. Indeed, midazolam-induced anesthesia resulted in repeated arousal during pharmacological loss of consciousness, which was distinguishable from spontaneous sleep states [17]. Moreover, the effect of midazolam on sleep varied by its applying frequency of application. Daily sedation interruption group, which used midazolam more frequently, exhibited 1) shorter total sleep time, 2) higher arousal frequency, and 3) longer REM sleep and Stage 3 and 4 sleep than continuous sedation group [18].

Benzodiazepines also significantly affect respiratory status of patients. Midazolam lowers the muscle activity during deep anesthesia, thereby increases the possibility of airway stenosis than it does in natural sleep. Genta et al. [19] noted that midazolam-induced sedation may increase collapsibility of upper airway muscle. On the other hand, diazepam possibly reduces sleep apnea and increases the percentage of NREM sleep in rats [20]. Also, Wedzicha et al. [21] stated that diazepam improved sleep duration in patients with chronic airflow obstruction. However, the usage potentially leads to adverse effects including hypothermia, tachycardia, hypertension, and partial memory impairment [22-24].

Intravenous Anesthetic Agent: Propofol and Ketamine

Propofol is one of intravenous anesthetic agents that has char-

acteristically short half life, thereby does not have prolonged effect [25]. However, it is observed to negatively influence patient's sleep after anesthesia by delaying sleep latency and reducing Stage 2 latency in drug-induced sleep [26]. To back up further, it exacerbated poor sleep quality of critically ill patients and reduced percentage of REM sleep [27]. Besides, there were conflicting findings that propofol improved sleep quality in patients in Intensive Care Unit [28]. In consistent with such findings, propofol therapy improved polysomnographic and Leeds Sleep Evaluation Questionnaire result of patients with refractory chronic primary insomnia [29]. Thus, in depth research is recommended to examine the effect of propofol infusion on sleep since it varies by circumstances.

However, propofol shows consistent postoperative outcome in patients with OSAS. According to the fact that propofol detters genioglossus activity [30], abundant studies have revealed that propofol infusion instigates significantly higher rate of airway collapse in dose dependent manner [30,31]. Along with the aforementioned results, the symptoms of OSAS measured by apnea-hypopnea index and oxygen desaturation level remained constant during the propofol sedation [32-36].

Ketamine is another intravenous anesthetic agent that affects sleep significantly. Some studies have found that ketamine helps NREM sleep, especially SWS both in animal model and patients [37,38]. Indeed, it increased slow wave for the first night

Table 3. Effect of commonly used sedatives and analgesic drugs on sleep

	Substance	Consequence
Benzodiazepines	Midazolam and	Reduce sleep onset latency
	Diazepam	Worsen sleep quality Reduce later stage of SWS Increase airway collapsibility
Intravenous anesthetic agent	Propofol	Varies by circumstances May improve or exacerbate poor sleep quality Increase airway collapsibility
	Ketamine	Increase SWA Reduce number of awakenings Induce psychotropic side effects during sleep Avoids respiratory events
Analgesic Agent	Opioids	Worsen sleep quality Reduce SWS and REM sleep Increase Stage 1 sleep May induce respiratory suppression Favorable effect on patients with periodic limb movement
Benzodiazepine antagonist	Flumazenil	Improve sleep quality Increase sleep efficiency and SWS Treat EDS and hypersomnolence Unfavorable effect on sleep deprived patients No effect on respiratory pathway
Other Adjuvant	Dexmedetomidine	More aroused after anesthesia Avoids respiratory events

SWS: slow wave sleep, REM: rapid eye movement.

of usage, while it subsequently increased total sleep and reduced number of awakenings for the second night [39]. However, it also demonstrated deleterious impact on sleep electrophysiology by inducing psychotropic side effects and unpleasant dreams during drug-induced sleep [40,41]. In case of cats, it triggered hallucination due to malfunction in central nervous system [42].

Mounting evidence has suggested that ketamine favorably acts on respiratory tract during anesthesia. Studies on pharmacology of ketamine indicate that it alters airway muscle movement and tranquilizes respiratory activity by reducing the release of acetylcholine in medial pontine reticular formation [38,43,44]. In rat model, ketamine has found to be doing so by increasing viscoelasticity of lung and influencing alveoli [45]. Aforementioned results demonstrate ketamine as a promising sedative for the patients with OSAS because it highly avoids respiratory events during anesthesia [46,47].

Analgesic Agent: Opioids

Opioid is an analgesic agent frequently used as pain reliever. There have been contentions about the effect of opioids on sleep, whether it is beneficial or not [48]. Meanwhile, many studies have implied that opioid has detrimental effect on sleep. Polysomnographic results and sleep diaries of opioid dependent patients have suggested that opioid is linearly correlated to poor sleep quality and reduction of SWS [49,50]. A significant decrease in SWS is highly liable to opioid, because opioid antagonist (naloxone) application successfully revitalizes SWS [51]. Disadvantageous consequence of opioid on sleep also has been recognized in other sleep stages. For instance, it significantly reduces REM sleep and increases Stage 1 sleep by impeding acetylcholine release in medial pontine reticular formation [51-54].

As respiratory depressant, opioid also detrimentally affects sleep disordered breathing and thereby increases number of awakenings. Numerous studies have exposed high correlation between opioid and respiratory deficiency, such as central sleep apnea and hypoxemia [52,55-64]. The severity of respiratory obstruction increases in dose dependent manner [56,65].

However, we need to consider that the patients who receive opioid prescription already have low quality of sleep as a result of pain. Mostly pain causes higher number of arousal, thus patients may accommodate daytime sleepiness and napping regardless of opioid [66,67]. Indeed, Cronin et al. [68,69] indicates that poor sleep quality has maintained even after opioid has been removed from patients. He also articulates that there has been no incident of airway obstruction when patients without OSAS used opioid [68]. Additionally, one review article even states that opioid analgesia significantly improves the sleep quality of patients [70]. For instance, opioid has been found to be a useful treatment of restless leg syndrome or periodic limb movement [71]. In several studies, opioid significantly reduced periodic limb movement index and increased percentage of

SWS [72,73].

Benzodiazepine Antagonist: Flumazenil

Benzodiazepine antagonist such as flumazenil deters sleep and increases alertness through GABAergic pathway [74]. Thus, it is commonly applied in order to reverse sedation during the recovery after anesthesia. Extent research has disclosed that flumazenil treated hypersomnolence or excessive daytime sleepiness by improving nocturnal sleep quality. Specifically, polysomnographic outcome reveals that flumazenil increases sleep efficiency and SWS, and reduces sleep onset latency [75,76]. However, for the sleep deprived patients, it rather lengthens sleep onset latency and disturbs SWS [77]. Moreover, according to the study conducted by Schönhofer and Kohler [78], it has no effect on respiratory pathway thus can be applied to the patients with OSAS.

Other Adjuvant: Dexmedetomidine

Dexmedetomidine is common adjuvant used in the process of anesthesia. It is an antagonist of the α_2 -adrenergic receptor, engendering the sedation that resembles sleep Stage 2 [79,80]. Alike most of analgesic drugs, it follows GABAergic pathway and shares a common biological pathway with natural sleep [79]. Since it maintains high level of thalamic connectivity, patient anesthetized with dexmedetomidine tends to be more aroused after the surgery [81].

As well as ketamine, it is known to provide sedation without the risk of respiratory depression. The need for artificial airway support during anesthesia has been significantly less in dexmedetomidine than that in other analgesic drugs [82]. Therefore, it is beneficial to patients with sleep apnea, especially children and adolescents who have unsettled airway [80].

CONSEQUENCES OF ANESTHESIA IN SLEEP DISORDERED PATIENTS

Sleep Deprivation

Since anesthesia and sleep share behavioral context, sleep deprivation is compensated during anesthetic state. Anesthesia alleviates fatigue and fatigue itself may further promote anesthesia vice versa [83]. In rat model, 12 hours of sleep deprivation led to more rapid loss of consciousness in sevoflurane-induced anesthesia [84]. Other studies that induced anesthesia with propofol or intralipid control in rats with sleep deprivation also have revealed similar outcome. After 6 hours of anesthetic process, sleep deprived rats did not demonstrate any distinguishable deprived characteristic in REM sleep and NREM sleep [83]. Isoflurane, desflurane and halothane also successfully supplemented sleep deprivation, while isoflurane and desflurane compensated NREM sleep debt twice faster than that of propofol [84-86]. However, in the case of inhaled anesthetic agent

(halogenated ethers), the anesthetic state was subsequent to NREM sleep, and REM sleep debt was not compensated [87]. Clinical trials with healthy persons were not significantly different with aforementioned outcomes. Induction of isoflurane reduced sleepiness and increased Stage 2 sleep in sleep deprived patients [88]. As it can be seen in multiple animal and human models, sleep deprivation complementation varies depending on the analgesic drugs.

Narcolepsy

Narcolepsy is a sleep disorder mostly characterized by intolerable excessive daytime sleepiness, cataplexy, and orexin deficiency. Orexinergic neurons are most divergent at wake state and generally remain low during sleep. Since it is highly correlated with gamma waves and muscle activity, an abnormality in orexinergic signaling pathway causes narcolepsy [89].

Several studies have concordantly delineated that orexin and analgesic drugs are highly correlated. Kushikata et al. [90,91] have indicated that barbiturates possibly target orexinergic neurons. Moreover, when orexin was injected to the cortex, the anesthetic effect of propofol was reduced [92]. Hypothetical mechanism is that orexinergic system promotes arousal under propofol-induced anesthesia, which is mediated by noradrenergic and dopaminergic neurotransmission of the cerebral cortex [93]. Likewise, when orexin was injected into the basal forebrain of anesthetized rats, they were alert and the time to fully anesthetize them was reduced [94,95]. Conversely, the activity of orexinergic neurons reduced in rats injected with sevoflurane and isoflurane [96]. Interestingly, this phenomenon did not appear when halothane was injected, suggesting that halothane-induced anesthesia did not participate in orexinergic signaling pathway [97]. Following issue is anesthesia in narcolepsy patients would look different from that in normal patients. Indeed, patients with narcolepsy have demonstrated similar intraoperative course and recovery period that are similar to healthy controls [98]. Also, their risk of postoperative complications have not been significantly higher than that of other groups [99]. To back up further, propofol and remifentanyl have been found to be safe during heart surgery in narcoleptics [100]. Besides, Hu et al. [101] listed some recommendations for the clinicians who are performing anesthesia on narcoleptics. In general, when anesthesia is conducted to patients with narcolepsy, sedation should be prevented and the treatment of narcolepsy should be continued until the day of operation. Use of short-acting anesthetics, such as propofol and remifentanyl, is recommended [101]. It is also necessary to pay attention to the interaction with the patient's existing drugs, such as stimulants such as modafinil [101]. Meanwhile, bispectral index monitoring is advantageous to preserve sevoflurane concentration at a reasonable level and to observe changes in status which are due to oversedation and preoperative drug use [101]. Furthermore, studies on mice with orexin deficiency have indicated that the

control of temperature is important in patients with narcolepsy during anesthesia [102]. For neurosurgical anesthetic operations involving the hypothalamus or the third and fourth ventricles, postoperative symptoms of narcoleptics should be checked after the surgery [103].

Circadian Rhythm Disorder

Patients conceivably experience sleep disturbances after anesthesia because anesthesia distresses circadian rhythm after surgery. Both animal and human models have shown that anesthesia impedes the rhythm of the daily cycle and changes the molecular clock. Recent study has displayed that sevoflurane-induced anesthesia suppresses the expression of clock genes [104]. Also, benzodiazepines influence the major neurotransmitter systems, which is associated with circadian rhythm control [105]. Plenty of studies have revealed that diurnal rhythm would be interfered when an animal is anesthetized during its active time [106]. However, much more evidence is needed to validate how anesthesia-induced change in the molecular clock renders change in behavior.

Disruption of circadian rhythm after anesthesia is heavily correlated to melatonin, an important agent that maintains circadian cycle. In fact, the level of melatonin metabolites has been increased while that of cortisol has been decreased after anesthesia [107]. Hence, melatonin is commonly used as a stabilizer when performing surgery with anesthesia. Oral administration of melatonin to patients undergoing local anesthesia has provided satisfactory surgical conditions due to anxiolytic effects, pain relief, and reduction of ocular motility disorders [108-110]. Indeed, a study illustrates that oral melatonin reduces the incidence of excitement after sevoflurane anesthesia [111]. Furthermore, several study approaches have presented that melatonin acts to mitigate apoptotic neurodegeneration caused by anesthesia. A study conducted on rats that were exposed to pro-apoptotic anesthesia cocktail (such as midazolam, isoflurane, and nitrous oxide) for seven days has reported that their anesthesia-induced brain damage significantly decreased after the application of melatonin [112,113]. In conclusion, melatonin is an effective treatment to reduce patient anxiety, to reduce the pain associated with hemostasis, and to improve preoperative damage before and after anesthesia [114].

Periodic Limb Movement Disorder and Restless Legs Syndrome

Abundant research has studied the correlation between anesthesia and abnormal movement in legs. They have denoted that spinal anesthesia spurs or worsens malfunction in motor activity, thereby leading periodic limb movement disorder (PLMD) or restless legs syndrome (RLS) [115-118]. Several anesthesia-related PLMD cases have implied that anesthetic agents affect spinal cord and hemocele [116,118]. Historically, benzodiazepines and ketamine have been applied as anesthetic agent and

treatment for PLMD and RLS [119,120]. However, among anesthetic drugs, opioids have been disclosed as the most influential for the disorder [121].

Obstructive Sleep Apnea

As we have delineated in previous section, several anesthetic agents and sedatives significantly disturb respiratory tract. Post-operative adverse risks are severe and recognizable in patients with OSAS [122]. Indeed, opioids and some sedatives potentially increase respiratory events, thereby should be excluded in surgery [123]. Thus, it is clinically crucial to acknowledge the effect of anesthetic drug on OSAS. Compensating such need, several group of researchers have published consensus statement or reviews for anesthesia in obstructive sleep apnea (OSA) patients, emphasizing the significance of comprehensive diagnosis of OSAS and reiterating avoided drugs before anesthesia [124-126].

CONCLUSION

Most analgesic agents and sedatives associated with anesthesia act on several brain regions involved in the initiation and maintenance of natural sleep. Since both anesthesia and sleep share biological mechanism via GABAergic pathway, they significantly impact each other. This may engender neurological damage and aforementioned sleep disorders, such as circadian rhythm disorder, PLMD, OSA. In order to avoid such adverse effects, acknowledging the consequence of anesthesia on sleep is clinically essential. Moreover, discovering thorough correlation between sleep and anesthesia potentially instigates novel therapeutic analysis. As stated above, analgesic agents possess a capability to be a desirable treatment of sleep disorders, and possibly vice versa. Thus, collaborative research in sleep and anesthesia opens new research avenues in both fields of study.

Conflicts of Interest

The authors have no financial conflicts of interest.

Authors' Contribution

Conceptualization: Hong SC. Project administration: Hong SC. Supervision: Hong SC. Validation: Hong SC, Kwon SY. Writing—original draft: Song JH. Writing—review & editing: Um YH, Kim TW, Kim SM, Kwon SY.

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