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Effects of Medications on Pupillometry Measurements of Sedation in the Intensive Care Unit

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Abstract
Administration of sedatives and opioid analgesics to hospitalized patients in the Intensive Care Unit (ICU) is a common event as part of the usual process of care. Accidental over-sedation leads to increased patient harm, prolonged ICU length of stay, and increased healthcare costs. Thus, clinicians must find efficient, objective ways to monitor patients' neurologic status and the effects of sedating medications. The Pupillary Light Reflex (PLR) and pupil size have traditionally been used for this clinical assessment. Digital Video Pupillometry, or Digital Pupillometry (DP), is emerging as a potential mechanism for more objective monitoring of analgesia and depth of sedation. DP provides rapid and precise electronic measurements of baseline and constricted pupillary diameters, velocity of contraction, and latency time between light exposure and onset of contraction reflex. Further research on the many effects of medication on PLR is needed in order to continue researching the utility of DP for reliable monitoring of ICU sedation. In this paper, we will discuss the known effects of various medication classes on pupillary musculature as reported in the current literature.

Key Terms:
- Digital Video Pupillometry
- Pain and Sedation Assessment
- Pupillary Light Reflex

Background

For nonverbal patients such as small children, intubated intensive care unit (ICU) patients, and those with neurologic deficits, it is often challenging to assess pain responses and sedation levels. Researchers and clinicians have become increasingly aware of the urgent need to develop and enhance ways of monitoring sympathetic and parasympathetic neurologic activity via pupil responses. Digital Pupillometry (DP) is emerging as a potential mechanism of objective monitoring of analgesia and depth of sedation, though further studies are needed to fully understand how commonly administered therapeutic medications may affect this measurement.

The autonomic nervous system is responsible for regulating pupillary musculature, thus controlling the amount of light that enters the eye. Respectively, the sympathetic and parasympathetic branches of this system dilate and constrict the pupil through specific muscle innervation in the eye. The pupillary light reflex pathway involves signal transmission between the retinal ganglion cells, optic nerve, midbrain, and short ciliary post-ganglionic nerves (Chanques et al., 2006). To begin this process, light is perceived by the photosensitive retinal ganglion cells. The optic nerve then receives this information and refers the message to the midbrain. In response, outward stimulation through post-ganglionic ciliary nerves contracts the circular muscle of the eye [Figure 1].

Pupillary Light Reflex (PLR) and pupil size have been traditionally used as clinical assessments of neurologic status. In standard clinical practice, the PLR is estimated using terms like “brisk,” “sluggish,” or “non-reactive,” where generally, a decrease in a patient’s level of arousal is associated with a decrease in pupil diameter and PLR response velocity (Martínez-Ricarte et al., 2013). Pupillometry has, until now, been difficult to objectively quantify. Standard manual clinical assessments of pupil size and reactivity conducted using a penlight have a high rate of error and inter- and intra-observer variability (Teasdale & Knill-Jones, 1978; Wilson, Amling, Floyd, & McNair, 1988).

The development of the portable, cordless, handheld digital pupillometer has enabled more sensitive and objective measurements of PLR and pupil size, potentially increasing the clinical utility of the assessment. The digital pupillometer utilizes a standard light source intensity to stimulate the PLR. The device then records the size of the pupil, the latency of response to light, the rate of change (velocity) of pupillary diameter, and the minimum and maximum diameters of the pupil (PLR amplitude) (Fountas et al., 2006; Martínez-Ricarte et al., 2013). DP is more sensitive than the unaided human eye, and studies have shown the digital pupillometer to identify minimal PLR that might otherwise mistakenly be considered “non-reactive” (Larson & Muhiudeen, 1995).

The new science of DP might offer a more objective measure of pain or analgesia, especially in settings where postoperative pain can be difficult to communicate. For example, in the ICU, many patients will relate pain scores that are inconsistent with their behavior which can lead to under- or over-sedation (Larson & Sessler, 2012). Adverse effects of untreated post-operative acute pain include limited mobility, impaired ventilation, and increased stress hormones. Conversely, overtreatment can lead to respiratory toxicity and aggravates opioid-induced side effects such as nausea and vomiting, ileus, sedation, and hyperalgesia (Larson & Sessler, 2012).

To clarify, pupillary dilation response is not specific for pain, but rather it is related to any stimulus that is strong enough to increase the level of arousal. Numerous clinical conditions,

medications, and variables, such as the patient's wakefulness, level of ambient light, and time of day that a procedure is performed, may alter pupillometry data collection. In order to validate the dependency of these methods, clinicians must consider that pupil size and pupillary response to pain are influenced by various factors besides pain.

In this paper, we will discuss the effects of certain medication classes on pupillary light reflexes, focusing mostly on opiates and sedatives. Based on a review of literature exploring the effects of medications on PLR in controlled environments, it is clear that DP technology will require health professionals to better understand the limitations and potential extraneous variables that may affect its measurements. This information is foundational to future studies of potential applications, patient care benefits, and advanced pharmacotherapy in uncontrolled environments like the ICU.

Opiates

Opioids and opioid-like medications have the ability to affect pupillary diameter, specifically by producing miosis of the eye and latency in the PLR. Opioids produce miosis by causing an excitatory action on the parasympathetic innervation of the pupil (Fleigert, Kurth, & Göhler, 2005). When light hits the retina of the eye, it elicits a response that must go through neural pathways in order to reach the brain for interpretation [Figure 1]. The Edinger-Westphal nucleus is one of those pathways. It is a nucleus of neurons that regulates parasympathetic signals to the iris muscles. Parasympathetic signals in the iris will result in miosis. Opioids suppress the inhibitory tract of this nucleus, resulting in more of an excitatory response that leads to what can be seen as pupil constriction. Furthermore, opioid induced miosis occurs in a dose-dependent fashion, with higher levels of plasma concentrations leading to more profound effects on pupil dilation. Several studies have utilized pupillometry to demonstrate the aforementioned effects of opioids.

Fleigert, et al. (2005) utilized pupillometry to study the pharmacodynamic effects of tramadol, an opioid-like drug, on PLR. In the study, the polymorphism of CYP2D6, a member of the cytochrome P450 enzymes involved in the metabolism of drugs, was analyzed in each participant (n=26) because this enzyme mediates the active O-demethylated metabolite of tramadol, which is responsible for providing its analgesic. Once healthy participants were labeled as extensive metabolizers (EM), intermediate metabolizers (IM), or poor metabolizers (PM), they received oral doses of 150 mg, 100 mg, or 50 mg tramadol and placebo, respectively. DP then captured the amplitude, latency, and duration of reaction to light pre-dose and post-dose.

The pharmacodynamic effects of tramadol were detected using digital pupillometry, and the CYP2D6 genotype highly influenced these responses. The miotic reaction was observed in all participants. However, there were differences in the extent of miosis observed between the differing metabolizers. The maximum mean differences between placebo and tramadol doses given to PM, IM, and EM were reported as -0.5 mm, -0.8 mm, and -1.1 mm, respectively (Fleigert et al., 2005). The lack of miosis in the PM compared to EM can be attributed to the fact that there is a lack of formation of the active O-demethylated metabolite of tramadol.

Furthermore, parameters of dynamic pupillometry were also studied. For both EM and PM, a decrease of amplitude, velocity of constriction, and reaction duration occurred, while an increase in latency was observed. However, the EM experienced these effects for a

much longer time period than the PM, 24 and 8 hours respectively (Fleigert et al., 2005). Therefore, these effects would be important to consider when using a DP to assess patients receiving tramadol in a clinical setting.

While the aforementioned studies have confirmed that opioids are capable of inducing miosis of the pupils and delaying response of the light reflex, one particular study questioned whether these effects would continue during opioid-induced toxicity. Rollins, Feiner, Lee, Shah, and Larson examined the effects of significant opioid-induced respiratory depression with accompanying hypercarbia and hypoxia. The sympathetic nervous system is activated during states of hypercarbia and hypoxia. Theoretically, this would cause the pupils to be overcome by sympathetic activation as well, causing mydriasis (dilation) of the pupils.

Rollins' study was designed to determine whether or not the sympathetic nervous system predominates, which would signify if the light reflex remains quantifiable during opioid toxicity with associated hypercarbia and hypoxia (defined as less than 85% Oxygen saturation). Ten healthy volunteers received remifentanil, a potent short-acting opioid analgesic as a gradually increasing infusion rate followed by intermittent boluses until an oxyhemoglobin saturation of 85% or less was reached, signifying hypoxia and hypercarbia had been reached. Arterial blood gases and pupillary measures were taken before opioid administration, at maximal desaturation, and fifteen minutes after recovery (Rollins et al., 2014).

Rollins' results demonstrated that during this time, respiratory rate was profoundly depressed and as expected, evidence of sympathetic activation was present, indicated by significant increases in heart rate (p-value=<0.0001). However, parasympathetic activation of the pupil remained, and all subjects were noted to have pupillary miosis occurring, with diameters of less than 3mm at the point of maximal desaturation (Rollins et al., 2014). Furthermore, the light reflex of the pupil was significantly diminished compared with pre-drug administration baseline measures. As the PCO2 levels increased, there was a decrease in PLR. This relationship shows that as CNS depression increases, the pupils are not as responsive to changes in light. Therefore, Rollins' study was able to establish that even during high-doses of opioid administration, parasympathetic effects of the pupil remain, which allows for pupillary examination and evaluation of PLR to remain useful for neurologic assessment during opioid toxicity.

GABA Agonists

In the ICU, benzodiazepines (e.g. lorazepam, diazepam, and midazolam) have traditionally been used to induce sedation in patients, especially as adjunct therapy in anesthesia. When combined with an opiate analgesic to achieve anesthesia, benzodiazepines run the risk of causing major respiratory depression, which calls for careful titration of the dose and constant monitoring of respiratory rate.

Hou, Samuels, Langley, Szabadi, and Bradshaw (2007) performed one DP study using either an orally administered placebo or diazepam 10mg, with either a sympatholytic or parasympatholytic eye drop, to observe the effect of benzodiazepines on the PRL and concluded that diazepam has no effect on pupillary reflexes. Another study performed by the same team compared pupillary function as affected by diazepam and diphenhydramine, again finding that diazepam has no significant effect on pupillary response (Hou et al., 2006).

Propofol is another common GABA agonist agent used for induction and maintenance of sedation in the ICU. When dosed

correctly, patients achieve a significant level of sedation with a rapid rate of recovery due to the drug's pharmacokinetic profile. A study performed by Odras-Banderas et al. (2014) examining pupillary response in patients where they were all sedated with propofol showed varied results. In post-operative heart surgery patients, all sedated with propofol, about half of the sample presented with no pupillary response during sedation. Neurological examination was normal in 80% of the sampled patients after sedation. The study concluded that propofol does alter neurological and pupillary response and suggested that these DP examinations should not be used to make clinical decisions on sedation management in patients on propofol.

Adrenergics

Dexmedetomidine, an alpha-2 adrenoceptor agonist, is a relatively new sedative agent gaining popularity due to its unique property of only producing mild cognitive impairment (Larson & Talke, 2001). Studies on animal subjects have found that alpha-2 adrenoceptor agonists reduce tonic inhibitory tone of cell bodies on the pupilloconstrictor neurons and inhibit the pupilloconstrictor nucleus via an alpha-2 adrenergic mechanism [Figure 1]. Although two opposing actions are occurring, the predominant effect of the pupilloconstrictor nucleus causes mydriasis to occur in both rat and cat subjects. The same mechanism of action occurs in humans with one difference: the effects of the pupilloconstrictor nucleus are not dominant to the effects of autoreceptors in human subjects; therefore, instead of mydraisis the subjects may experience miosis (Koss, 1986).

The Department of Anesthesia and Perioperative Medicine at the University of California tested this hypothesis on eight healthy control subjects (Larson & Talke, 2001). Dexmedetomidine was infused via a computer-controlled pump set to a target plasma concentration of 0.6 ng/ml to ensure adequate sedation. Measurements on pupil diameter and light reflexes were taken every two minutes starting thirty minutes before the administration of dexmedetomidine until the discontinuation of dexmedetomidine after 45 minutes.

Compared to the data collected pre-infusion, dexmedetomidine did not affect resting pupil diameter significantly, with pre- and post-demedetomidine pupil sizes measuring 2.0 $\pm$ 0.36 and 2.0 $\pm$ 0.32 respectively. However, dexmedetomidine increased the amplitude of the pupillary light reflex from 0.30 $\pm$ 0.14mm to 0.37 $\pm$ 0.12mm compared to pre-infusion values. The observed pupillary effects of dexomedetomidine on humans in the University of California's study did not coincide with previously seen pupillary effects in mice and rats given an alpha-2 agonist (Koss, 1986). Researchers concluded that pupillary effects of dexomedetomidine in human subjects should be studied further and cannot be explained via the pathway of alpha-2 inhibition from the locus coeruleus to the pupilloconstrictor nucleus as seen in animal subjects.

Other Influences

Documentation on external factors causing variations on pupillary reflexes can be found dated as far back as 1943, when Skoglund wrote about how alcohol dilates the pupil in proportion to blood alcohol levels. Hess and Polt (1966) found that pleasant taste induces pupil dilation. Loud noises have also been found to increase pupil diameter due to activation of the sympathetic pathway. Barlett, Faw, and Leibert (1967) discovered alertness in an individual presented with pupillary constriction, whereas relaxation was suggested by pupillary dilation (Sarbin & Slagle, 1979). The Federal University of Maranhao (Brazil) found that men and women with moderate to severe anxiety had greater pupil

dilation than those with mild to no anxiety, though there was no difference in pupil dilation between the genders (Bertrand, Garcia, Viera, Santos, & Bertrand, 2013).

When assessing pain in nonverbal patients in a realistic setting, it may be difficult to control external factors such as taste, anxiety, light level, and noise. Thus, it is important to investigate and understand patients' conditions and medications, along with the many other external factors that can affect a pupillometry reading, in future studies and clinical practices.

Conclusion

While sedation is frequently required for critically ill patients during routine procedures or to alleviate pain and anxiety, over-sedation has become a common and unfortunate occurrence. Many negative outcomes are associated with over-sedation, such as cardiovascular instability, immunosuppression, decreased gut motility, increased risk of thromboembolic events, and prolonged ICU stays. Unfortunately, a subjective scoring tool is currently used to monitor sedation levels, which has the potential to leave critically ill patients over-sedated and at risk.

Digital pupillometry is a promising tool that potentially is able to objectify the process of monitoring the depth of sedation levels in patients by relying on pupil diameter and pupillary light reflexes as markers of sedation levels. Before implementing the routine use of DP, it is important to consider any and all factors that may affect patients' pupil diameters and PLR. Medications that are commonly used to achieve sedation include general anesthetics, opiates, and benzodiazepines. Through previous studies, it has been shown that while opiates and anesthetics, such as propofol, do have significant implications on pupillary musculature, benzodiazepines do not. Unique factors to drug molecule such as metabolism and patient specific sympathetic activation to external stimuli also play a critical role in interpreting sedation levels. Therefore, clinicians should be vigilant and use clinical judgment as we learn more about DP. Further research is vital in order to establish the potential of implementing the use of DP to supplement current sedation scales, such as the Richmond agitation sedation scale, and to aid clinicians in objectively measuring sedation levels and neurologic status in the critically ill.

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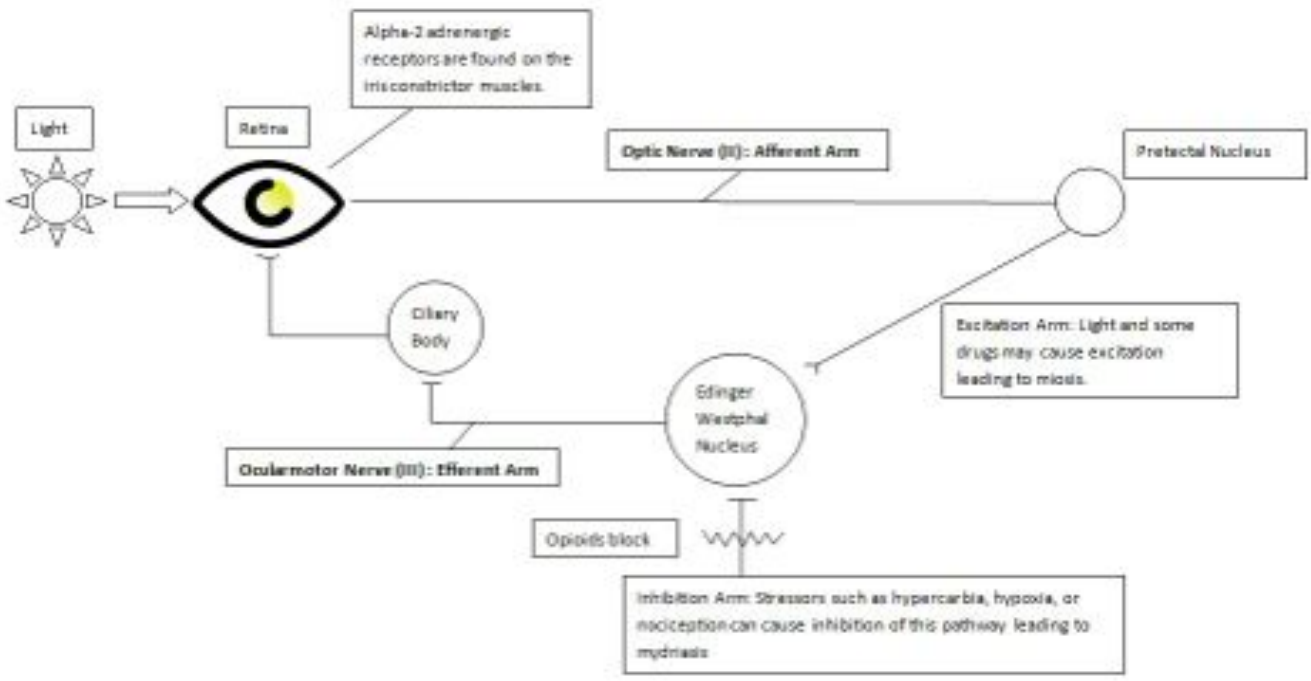

Figure 1: Pupillary Light Reflex Mechanism
(Illustration by Jeffrey Quach; adapted from Barrett, Barman, Boitano, & Brooks, 2016)

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