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Research report

Effects of mild to moderate sedation on saccadic eye movements

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HIGHLIGHTS

- We tested if the effects of sedatives on saccades are nonspecific or differ between sedatives.
- The dosages were selected for the subjects to report similar subjective levels of sedation (SLS).
- Propofol and midazolam had strong effects on saccadic dynamics, latency, and gain.
- Dexmedetedomidine had less impact on saccadic metrics and presented no changes in saccadic gain.
- Sympathetic system suppression differs from inhibitory GABA-A receptors activation at same SLS.

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ABSTRACT

Sedatives alter the metrics of saccadic eye movements. If these effects are nonspecific consequences of sedation, like drowsiness and loss of attention to the task, or differ between sedatives is still unresolved. A placebo-controlled multi-step infusion of one of three sedatives, propofol or midazolam, both GABA-A agonists, or dexmedetedomidine, an α_2-adrenergic agonist, was adopted to compare the effects of these three drugs in exactly the same experimental conditions. 60 healthy human volunteers, randomly divided in 4 groups, participated in the study. Each infusion step, delivered by a computer-controlled infusion pump, lasted 20 min. During the last 10 min of each step, the subject executed a saccadic task. Target concentration was doubled at each step. This block was repeated until the subject was too sedated to continue or for a maximum of 6 blocks. Subjects were unaware which infusion they were receiving. A video eye tracker was used to record the movements of the right eye. Saccadic parameters were modeled as a function of block number, estimated sedative plasma concentration, and subjective evaluation of sedation. Propofol and midazolam had strong effects on the dynamics and latency of the saccades. Midazolam, and to a less extent, propofol, caused saccades to become increasingly hypometric. Dexmedetedomidine had less impact on saccadic metrics and presented no changes in saccadic gain. Suppression of the sympathetic system associated with dexmedetomidine has different effects on eye movements from the increased activity of the inhibitory GABA-A receptors by propofol and midazolam even when the subjects reported similar sedation level.

Sedatives alter the dynamics of visually-driven saccadic eye movements between stationary targets. It is not known if these changes are nonspecifically linked to the sedated state of the subject, like drowsiness and loss of attention to the task, or if they also depend on the type of sedative. We measured the effects of three commonly used sedatives, propofol, midazolam, and dexmedetomidine, and of saline control on saccadic responses. Dexmedetomidine has a different pharmacological mechanism of sedation than propofol and midazolam, and therefore it is a potential candidate to verify if the effects on saccades are drug-specific. The intensity of "placebo effects" on saccadic eye movements inside a sedation study, where the subject does not know if receiving a sedative or saline, is not well quantified in the literature. Using the placebo group, we were also able to quantify how much of the observed changes in saccadic behavior during the session were associated with the experimental paradigm per se, most likely fatigue, boredom, and on-the-task learning, all being naïve subjects to oculomotor tasks inside a controlled laboratory setting. In some subjects, physical and/or psychological effects associated with the two IV needles might have also influenced the execution of the task

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and the overall number of blocks obtained from the subject. The finding of an irregular, but still very significant on average, increase in the self-reported sedation level inside the placebo group as the session progressed was also used as an additional tool in determining the importance of the subjective state of sedation on eye movements.

Propofol is widely used perioperatively to induce and maintain anesthesia and for procedural sedation. Midazolam is used to induce sedation and amnesia before medical procedures, for prolonged sedation in individuals receiving mechanical ventilation, and as anxiolytic. Both are agonists of the gamma-aminobutyric acid type A (GABA-A) benzodiazepine receptors. These receptors are present in several brain areas and have an inhibitory action on their target neurons. Ibotenic acid and its derivative muscimol, also GABA-A agonists, are commonly used for microinjections in experimental animals to induce a reversible inhibitory action on the targeted brain location. It is not surprising, therefore, that significant effects on the peak velocity of saccades were reported for propofol [1], midazolam [2,3], and diazepam [4]. Propofol was also found to reduce ocular microtremor [5,6], which is a small high frequency random tremor of the eyes linked to neural activity in the brainstem and midbrain reticular formation [7].

As third sedative we used dexmedetomidine, which is a selective α_2-adrenoceptor agonist [8]. Virtanen et al. [9] found that medetomidine – dexmedetomidine is the pharmacologically active d-isomer of medetomidine – has no binding activity with benzodiazepine receptors. By activating the inhibitory α_2-adrenoceptors both at the central level and at the peripheral sympathetic nerve endings, it inhibits, in a dose-dependent function, the release of noradrenaline, with a corresponding reduction in the sympathetic neural activity. It is commonly used as short-term sedative in mechanically ventilated critically ill patients, as adjunct to anaesthesia, and as sedative for invasive procedures. This drug has sedative, analgesic, and antishivering properties [10] without causing respiratory depression. The sedated patient remains cooperative [11], which is a critical factor in many procedures and makes it a highly desirable alternative, in several applications, to benzodiazepines. The brain area presenting the strongest attenuation of activity during dexmedetomidine sedation in rats is the locus coeruleus [12], the principal site in the brain for the synthesis of noradrenaline. Located in the rostral pons, it projects to several areas, including spinal cord, brainstem, cerebellum, hypothalamus, thalamic relay nuclei, amygdala, basal telencephalon, and cortex [13–16]. The main afferents to the locus coeruleus are from the paragigantocellularis and the prepositus hypoglossi nuclei in the rostral medulla [17,18]. The prepositus hypoglossi is part of the oculomotor neural integrator responsible for maintaining horizontal gaze [19] and its action on the locus coeruleus seems to regulate REM sleep [20]. Saccadic peak velocity is affected by dexmedetomidine [21]. Our study is the first to compare these three sedatives and saline in exactly the same paradigm configuration. We also determined the optimal concentration of each drug for single-dosage studies, i.e., the value that produced the strongest oculomotor effects at the group level with the majority of the subjects still able to perform the saccadic task.

1. Methods and procedures

1.1. Subjects

Sixty healthy volunteers (25 males, 35 females, age 19–56) were randomly assigned to one of four groups (placebo, propofol, midazolam, dexmedetomidine) of 15 subjects each. All subjects had a preliminary physical examination prior to the day of the test, and at the day of the test females were tested for pregnancy. Sedation monitoring followed the guidelines of the American Society of Anesthesiology, which include continuous evaluation of respiration and circulation using pulse oximetry, non-invasive blood pressure monitoring, and ECG. At the end of the session the subject rested for as long as necessary, and was released only when the accompanying person, identified by the subject at the beginning of the session, arrived at the clinic. Written instructions were given to the subject not to drive or do other potentially dangerous tasks for the remainder of the day. The study was approved by the University of Alabama at Birmingham Institutional Review Board (IRB) and it adhered to the tenets of the Declaration of Helsinki for clinical research. Subjects were previously informed about the experimental protocol and the possible effects of the sedatives and had signed an IRB-approved informed consent.

1.2. Protocols and data acquisition

All subjects were naïve to oculomotor tasks performed in a controlled laboratory setting and to the purpose of the experiment. After some saccadic training trials and a brief analog calibration of the eye signals, the subjects received computer-assisted infusions with a Graseby® 3400 infusion pump. The profile of the infusion rate was designed to stepwise increase the plasma drug concentration [22], with each step lasting approximately 20 min. The subject rested for the first 10 min to give time to the blood concentration to stabilize, and saccadic testing was carried out during the last 10 min of each step. At the end of the saccadic task, the subjects were asked to self-evaluate their level of sedation (SLS) by using a visual analogue scale of sedation ranging from fully awake (perceived sedation level 0) to very sedated (perceived sedation level 10), and a venous blood sample for verification of actual plasma concentration was obtained from an intravenous cannula on the arm opposite to the side of the infusion. The infusion was then stepped to the next target concentration. The sequences of rest/testing/SLS/blood-sampling (blocks) were repeated until the subject was too sedated to continue or for a maximum of 6 blocks. An average of 150–250 trials was acquired in each block. Subjects were unaware of what they were given and, during the initial block (BLOCK = 0), all subjects received a saline infusion in order to obtain the subject's baseline saccadic metrics. For the placebo group, the subsequent blocks continued to be saline. For the other three groups, the saline was replaced by the sedative, and the target blood concentration was set to double at each subsequent block. For dexmedetomidine, the set of target concentrations was 0.0125, 0.025, 0.05, 0.10, 0.20, 0.40, and 0.80 ng/ml. For midazolam it was 5, 10, 20, 40, and 80 ng/ml. For propofol it was 0.05, 0.10, 0.20, 0.40, 0.80, and 1.60 μg/ml. In order to take into account differences in individual sensitivity to the sedative, we varied the starting value of the target concentration between subjects. This assured that a sufficient number of subjects received their highest tolerable drug concentration, in terms of still being able to perform the saccadic task, between blocks #3 and #5. For example, some subjects in the propofol group had assigned target concentrations of 0, 0.05, 0.10, 0.20, 0.40 μg/ml, while others covered the 0, 0.20, 0.40, 0.80, 1.60 μg/ml values. The measured concentrations from the blood samples, using a gas chromatographic–mass spectrometric procedure, are illustrated in Fig. 1, together with the linear regressions that were used to compute the group-wide estimated blood concentration values (indicated in the plots by ×) at each target value, which were used in the subsequent statistical and model analyses (CONC values).

The subjects were seated in a hospital sleeper chair that was modified to carry a chin rest and two temporal pads to minimize head movements. The room was dimly illuminated by the room window and/or indirect light. A board with LEDs was placed in front of the subject at a distance of 80 cm. The board had