REDUCTION OF GAIN AND TIME CONSTANT OF VESTIBULO-OCULAR REFLEX IN MAN INDUCED BY DIAZEPAM AND THIOPENTAL

Serge Padoan, * Kari Korttila,† Måns Magnusson, * Ilmari Pyykkö, † and Lucyna Schalén *

*Department of Otorhinolaryngology, University Hospital of Lund, Lund, Sweden, Departments of †Anesthesiology and †Otolaryngology, University Hospital of Helsinki, Helsinki, Finland

Reprint address: Dr Serge Padoan, Department of Otorhinolaryngology, University Hospital of Lund, S-221 85 Lund, Sweden

Abstract — The effect of intravenous administration of two sedatives, diazepam (0.3 mg/kg) and thiopental (6.0 mg/kg), on the vestibulo-ocular reflex (VOR) in man was investigated on 9 volunteers. The VOR was evoked with a velocity step rotation test and gain and time constant of perrotatory and postrotatory nystagmus were measured. Both drugs reduced VOR gain. Diazepam-induced reduction lasted 8 h and thiopental-induced reduction 1 h. A reduction of the VOR time constant was found lasting about 1 h for both drugs, but with a tendency for the thiopental effect to last longer. These findings, not previously described in man, differ from what has been found in macaques and rabbits injected with diazepam. The reduction of gain and time constant were not correlated with the blood concentration of either drug.

The present results suggest that in man the VOR gain and time constant are both reduced by different types of sedatives although with different time courses. On the basis of previously shown effect of alertness on the VOR, it is hypothesized that diazepam and thiopental, besides having a specific effect on central nervous system structures important to the VOR, also induce reduction of the VOR through a general sedation of the CNS.

Keywords — VOR; diazepam; thiopental; time constant.

Introduction

Benzodiazepines and barbiturates are known to affect voluntary and reflexive eye movements in humans (1–4), and benzodiazepines are known to affect reflexive eye movements in animals (5–7). The neurophysiological correlate for this effect is presumed to be a depressant action on neurons important to eye movements (1,2,5–8). Nevertheless an unspecific effect of the drugs is also plausible, the possible mechanism being general depression of the central nervous system (CNS), causing reduction of alertness.

An effect of alertness on vestibulo-ocular reflex (VOR) gain has been described previously (9). Recently an effect of arousal on the velocity storage mechanism has been described, causing a prolongation of the time constant of the VOR in rabbit (10) and increasing optokinetic afternystagmus (OKAN) in man (11). Thus reduction of alertness due to CNS depression accomplished by benzodiazepines or barbiturates could be expected to reduce the time constant of the VOR.

To our knowledge no studies on the effect of benzodiazepines or barbiturates on the human VOR refer to the time constant. As animal studies (5,7) indicate an increasing effect of diazepam on the time constant and a reducing effect on gain with different time courses, it seemed important to test the validity of these findings in humans. Furthermore most studies on man have been performed with oral administration of drugs, while in animal studies drugs have been given intravenously. Besides species differences, time
courses may thus differ enough to make it difficult to compare results. In this experiment, doses were chosen corresponding approximately to those used in clinical practice for intravenous induction of anesthesia.

We also considered it clinically important to elucidate the effect of these drugs on reflexive eye movements and alertness, given the wide use of intravenous (i.v.) administration of benzodiazepines for short-term anesthesia of outpatients, who only a few hours after an operation may have to deal with complicated traffic situations.

The aim of the present study was to investigate the effect of i.v. diazepam and thiopental on VOR gain and time constant in man, and to probe the correlation of the effects with blood concentrations of the drugs.

Materials

Nine paid volunteers, 5 females and 4 males, age 22 to 38 (mean age 30.3), took part in the study. They were all healthy and had no history of vertigo or of any neurological or metabolic disorder. All had normal hearing, vision, and weight and were nonsmokers.

Methods

Each subject was tested 3 times at 2-week intervals, which enabled these drugs to be virtually eliminated between trials. On each test occasion, the subjects were assigned to diazepam, thiopental, or no drug according to a latin square design. No placebo was used, as the effects of the drugs were so obvious to the subjects. Both drugs were given intravenously in quantities equivalent to 0.3 mg/kg body weight for diazepam, and 6.0 mg/kg body weight for thiopental, corresponding to doses used for induction of anesthesia with thiopental and half that amount with diazepam (12). The drugs were given at 8 AM and the tests were performed at 9 AM, at noon, and at 4 PM.

Food intake was standardized for the participants and consisted of two cheese sandwiches and a cup of tea after concluding the tests at noon. Alcoholic beverages or any kind of drugs were forbidden during the 48 h prior to each trial.

Before each recording, blood samples were taken with a disposable cannula from a cubital vein in the arm contralateral to the arm in which the drugs were given. The samples were frozen and subsequently analyzed by gas chromatography for concentration of the respective drug. Because of incomplete blood collection, thiopental blood concentrations were analyzed in only 7 subjects at 9 AM and in only 8 subjects at noon and 4 PM.

The subjects were seated in a rotation chair, provided with an occipital support fixating the head in the center of the vertical rotation axis and with the ear–eye axis horizontal. Clockwise and counterclockwise (CW and CCW) rotation-induced vestibular nystagmus was achieved by 60°/s² acceleration and deceleration in darkness for 2 s each giving a velocity step of 120°/s. Rotation lasted 90 s. Eye movements were recorded with DC electrooculography (13).

Analysis

Starting from the first beat after reaching the plateau of each velocity step, the peak velocity of the slow phase of the nystagmus beat occurring every 5 s was calculated manually from the recordings. The mean of the slow phase velocity of the corresponding nystagmus beats from the 4 stimuli, ie, the velocity steps of acceleration/deceleration of CW and CCW rotation, was calculated. To these mean nystagmus velocities an exponential decay was fitted and the time constant was calculated by a computer (DEC Professional 380 with RS/1 software, Bolt Beranck & Newman, Cambridge, MA). Gain was calculated as the initial peak slow phase velocity divided by the velocity step.

Individual values of gain and time constant for each drug test occasion were normalized, ie, divided by their respective control value, to yield a relative value. This was done to avoid bias from possible variations in alert-
Figure 1. The relationship between drug concentration (thiopental or diazepam) and VOR parameter (relative gain or relative time constant). Individual values are indicated. Results for 9 AM, noon, and 4 PM are denoted by squares, circles, and triangles, respectively. The f(X) = 1.0 line represents the arithmetic control value. Means and standard errors of the mean from the three test occasions are indicated by the corresponding filled symbols connected by a line. (Figure continued on facing page.)

Improvement in correlation (Pearson's coefficient for a log-log fit at the 3 trials, ie, 9 AM, noon, and 4 PM, was 0.097, 0.039, and 0.113 between thiopental concentration and the time constant; 0.580, 0.488, and 0.456 between thiopental concentration and gain; 0.020, 0.640, and 0.136 between diazepam concentration and the time constant; 0.116, 0.482, and 0.241 between diazepam concentration and gain).
Discussion

In the present study two sedatives, thiopental and diazepam reduced human VOR gain and time constant. Apparently diazepam had a longer effect on the gain than on the time constant, while thiopental tended to show an opposite effect profile. In regression analysis, however, individual values of either VOR parameter were not correlated with blood concentrations of either drug.

A reduction of VOR gain by diazepam and thiopental is in accordance with most previous studies in man and in animals. The impairment of the VOR caused by both drugs is presumed to be a result of their effect on infratentorial neuronal populations of the central nervous system, in the case of diazepam,
in the vestibular nuclei (1–8,15,16). The VOR time constant in rabbits is prolonged by increased alertness (10) as is OKAN in man (11). Diazepam and thiopental may thus be expected to diminish gain and, by sedation, to shorten the VOR time constant.

Differences between Humans and Animals

There are few previous reports on the effect of sedating agents on the VOR time constant. In the macaque, diazepam reduces gain but increases the VOR time constant (5). In the rabbit the same drug does not seem to affect the time constant although it reduces gain (6,7).

The difference between these findings and our results in man, with a clear reduction in VOR gain and time constant, may be due to the differences between the species studied, the amount of drug given, and to the intervals chosen for measuring the VOR.

Very little sedation was reported in the macaque, though 0.7 mg/kg diazepam was used (5). This can be compared to the present 0.3 mg/kg, which clearly causes sedation in humans. Furthermore, gaze nystagmus was noticed immediately after injection of diazepam on macaques. We observed no pronounced gaze nystagmus after diazepam and a transient gaze nystagmus after thiopental, which is consistent with previous reports (17). In the rabbit experiment (7), 0.6 mg/kg diazepam was used and one group of rabbits showed excitatory response in VOR.

Furthermore, the first test of the VOR function in the present human experiment could not be done until 1 h after injection because the subjects were simply unable to cooperate earlier. In the above mentioned experiment on macaques, VOR tests were com-

Figure 2. The difference between the effect of two drugs on the two VOR parameters at the two later measurements, thiopental affecting the time constant more than diazepam and diazepam affecting gain more than thiopental. Error bars indicate standard error of the mean.
Reduction of Gain and Time Constant of VOR

Menced only 5 min after injection and the effect on the VOR time constant lasted less than 1 h (significantly only 16 min), while the effect on gain lasted several hours. In the rabbit experiment, tests also started shortly after injection and gain was significantly reduced for 1 h.

Moreover, one should bear in mind that the pharmacological profile of benzodiazepines varies between species to the extent that in some cases alertness instead of CNS depression is achieved (18). In a study of benzodiazepine binding in human brains (19), a good correlation has been shown between in vitro inhibition of (3H)flunitrazepam binding to human cerebral cortex homogenate and in vivo tests of pharmacological potency of several benzodiazepines in humans, while correlation with in vivo potency tests on monkeys was low.

A common finding in our study and in the animal experiments mentioned above is that benzodiazepines affect VOR gain and time constant with different time courses. The interpretation of Blair and Gavin (5); that this could be due to diazepam having multiple sites of action, is plausible. In our experiment thiopental also tended to have different time courses in its effect on the 2 parameters of the VOR, but in a fashion opposite to that of diazepam.

Possible Contributing Effect of Sedation

To some extent benzodiazepines and barbiturates share sites and mechanisms of action in the CNS (18). Benzodiazepine binding is low in the human brainstem and intermediate in the cerebellum (19), which has extensive projections to and from the vestibular nuclei (20). Nevertheless, the reticular formation and the vestibular nuclei are both located in the brainstem and seem to be major sites of the CNS depressant action of benzodiazepines (21,22). However, the VOR has also been shown to be influenced by mental activity (9,23). Thus diazepam or thiopental could also affect the VOR either by reducing alertness and/or by acting on higher centers of the CNS disrupting the ability to choose a frame of reference, the latter known to be of importance when willingly modulating the VOR (23).

Lack of Correlation between Drug Concentration and Effect

There seems to be some controversy regarding the correlation between serum levels of benzodiazepines and peak velocity of voluntary saccades (24,25). The apparent lack of correlation between the effect of the diazepam and thiopental on the VOR and their concentration in blood, as observed in the present study, might be explained by individual variations in pharmacokinetics and pharmacodynamics of diazepam and thiopental (26–28). Furthermore, large interindividual variations in the VOR, as found in the present experiment, make it necessary to investigate larger groups of subjects to demonstrate any possible significant correlation.

Conclusions

The effects of two sedatives, diazepam and thiopental, on the human vestibulo-ocular reflex were investigated in the present study. VOR evoked by a velocity step was reduced by both drugs. But while diazepam-induced reduction of gain lasted up to 8 h, thiopental was only effective for 1 h. The time constant was only reduced for 1 h by both drugs, although thiopental-induced reduction tended to last longer.

Different sedating agents are thus demonstrated to have different profiles in their reduction of the human VOR. Both specific and unspecific action in the brainstem due to sedation may be responsible for the impairing effect of diazepam and thiopental on the human VOR.

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