Pupillometry in the Detection of Concomitant Drug Use in Opioid-Maintained Patients

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SUMMARY

Pupillometry and ocular response measures are sensitive to a variety of acutely administered drugs and as such are useful for drug detection and fitness-for-duty applications. The utility of pupillometry to complement urine testing in methadone clinics, where there is considerable non-therapeutic drug use, has not been tested. A video-based pupillometer (FIT 2000) was evaluated in 37 opioid-maintained patients. Three times a week they provided urine samples and pupillometry measures of: initial diameter (ID) in mm; constriction amplitude (CA) in mm; constriction latency (CL) in msec; and saccadic velocity (SV) in mm/sec. Analysis of the success rates indicated that 92.9% of subjects obtained an acceptable reading, 59% on the first attempt. Low variability in pupillary parameters on drug-free days are necessary for effective identification of concomitant drug use. The variability (standard deviation) of ID (0.51 vs. 0.68), CA (0.12 vs. 0.27) and SV (7.2 vs. 11.1) increased on days when the urine was positive for abused drugs compared with drug-free urine days in subjects (n = 6). Subjects who were always drug-free (n = 4) had lower variability than those who always had urine positive for additional drugs (n = 20). These preliminary results suggest that pupillometry may be useful to verify concomitant drug use in a methadone-maintained population. Successful implementation of the methodology could reduce costly and intrusive urine testing. © 2004 Prous Science. All rights reserved.

Key words: Drug detection - Methadone-maintenance - Pupil diameter - Pupillometry - Saccadic velocity - Urinalysis

INTRODUCTION

Many centrally-acting drugs are known to affect pupil diameter, the light reflex and the ability to track a moving target through smooth pursuit or saccadic eye movement (1-4). For example, opiates constrict the pupil and diminish the light reflex (5-8), stimulants dilate the pupil and have variable effects on the light reflex (4) and marijuana smoking obunds the light reflex (3). The pupillary effects of drugs have typically been defined in placebo-controlled laboratory studies where only a single drug was administered. However, pupillary effects and eye tracking after drug administration while patients are maintained on other drugs have not been studied. It is uncertain how the presence of one or more treatment medications influences the pupillary responses of additional drugs.

Recently-developed pupillometers capture both static (e.g., pupil size) and dynamic (light reflex parameters, saccadic and smooth pursuit eye movement) pupillary and ocular responses. These instruments have been proposed for diverse applications including drug detection and fitness for duty assessments. Such instruments are very sensitive in determining changes in pupillary parameters in patients that are drug free. However, their ability to detect changes in patients chronically treated with centrally acting drugs that affect pupillary size is uncertain. In the present study, a new automated instrument, the FIT 2000, manufactured by Pulse Medical Instruments (PMI, Inc.; Rockville, MD, USA) that safely and quickly measures pupillary function was evaluated in opioid-maintained patients. We also tested the stability of pupillary measures, the ease of operation and practical feasibility of using pupillometry in a minimally supervised methadone maintained poly-drug using population.

METHODS

Participants

We invited 37 patients enrolled in studies at NIDA Archway clinic, a treatment research facility, to participate in this study. To qualify for the study, participants had to be healthy individuals, over 18 years of age, dependent on opiates and willing to attend counseling and daily clinic visits. There were no exclusions other than those imposed by the primary study (e.g., pregnancy, allergies to study drugs) (9). The subject population included 21 males and 16 females; 68% of the participants were
African Americans and 32% were Caucasian. The average (± SD) of the male participants was 42.7 years (± 10.2). The average age of the female participants was 40.3 years (± 5.6). The participants had extensive drug abuse histories that included current opioid dependence, chronic cocaine use and frequent use of other illicit drugs. They were maintained on methadone in doses that ranged from 70 to 100 mg per day. Two participants were maintained on buprenorphine (16 mg per day).

Procedure

Each participant signed a consent form approved by the NIDA Institutional Review Board that described the study, its risks and benefits. After agreeing to participate, the operation of the pupillometer was explained and demonstrated to the research volunteers. They were allowed to practice the test sequence in the presence of the administrator until they obtained a successful test sequence. This single exposure was the only supervised orientation the participants received.

Participants used the pupillometer on a maximum of three occasions each week, always on days (usually Monday, Wednesday and Friday) when the protocol of their primary study required that they provide a urine sample for drug testing. Urine was analyzed onsite, using the OnTrak Teststik (Varion Diagnostic Inc, Lake Forest, CA, USA), for: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana metabolites, phencyclidine and opiates. Subjects were compensated for successful pupillary tests with a $2 coupon redeemable at a fast food restaurant chain.

Pupillometer

The pupillometer uses low levels of infrared radiation to illuminate the pupil. It has been extensively tested over the past eight years with over 1.6 million tests performed on over 34,000 individuals in 68 different sites (PMI internal documents). There have been no reported medical problems or complaints. It is in compliance with all FDA guidelines for Class 2 ophthalmic devices and within standards for infrared exposure limitations.

On study days, room lights were kept at a constant illumination. Participants were assigned a unique identification number that was entered into the instrument before enrollment into the study. Participants accessed their file by entering their identification number. The subject stood comfortably in front of the instrument and looked through the viewing lens with one eye (left) while the other eye was open at all times. The pupillary test sequence was initiated when the participant pressed a start button. A green LED target quickly moved horizontally across the viewing screen. Saccadic velocity (SV) data were collected at a rate of 750 Hz during this phase. The target then paused in the middle of the viewing field and a series of light flashes ensued. Initial pupillary diameter (ID) (measured before the flashes), constriction amplitude (CA) and constriction latency (CL) were collected at a rate of 60 Hz. If the test was successful, a high pitch tone sounded and a printer yielded a paper copy of the four measured parameters. If the instrument lost eye tracking, or if for any reason data could not be collected, a low tone sounded, a fault message was given and the test was aborted. If tracking was lost during the light reflex phase, the stimuli were repeated up to 6 times before the sequence was aborted and a fault was recorded. After a fault message, the participant could reinitiate a test sequence by reentering their identification number. A successful test sequence (no repeat flashes) lasted about 30 sec. Subjects repeated the test sequence until they obtained a successful result.

Analyses

The data were analyzed to determine the feasibility for use in this patient population. The number and percentage of successful tests and unsuccessful tests (faults) were summarized for each participant.

Pupillary data from days where there was no evidence of other recent drug use (urine negative for abused drugs) were compared with days where there was evidence of recent drug use (urine positive). These comparisons were carried out using both within-subject and between-subject tests. A drug-free baseline was determined for subjects who provided negative urine on more than 10 days. The four parameters were used to determine the Goodness-of-Fit calculation as follows:

\[
Index = \left( \frac{\mu_{ID} - \mu_{ID}}{\sigma_{ID}} \right)^2 \odot \left( \frac{\mu_{CL} - \mu_{CL}}{\sigma_{CL}} \right)^2 \odot \left( \frac{\mu_{CA} - \mu_{CA}}{\sigma_{CA}} \right)^2 \odot \left( \frac{\mu_{SV} - \mu_{SV}}{\sigma_{SV}} \right)^2
\]

where ID, CL, CA and SV are the value of the parameters on any particular pupillary screening, \( \mu \) represents the mean baseline value and sigma is the baseline standard deviation of each parameter. After a baseline was established for each participant, a Chi square analysis with 4 degrees of freedom was calculated (FIT index) for subsequent drug-positive days. This result was referenced against the critical Chi square values table \( (p = 0.1, \chi^2 = 7.78, p = 0.01, \chi^2 = 13.28) \). These calculations yielded the probability that the particular reading differed from the established baseline.

Finally, pupillary parameters in participants who always gave negative urine were compared with those who always gave positive urine to determine whether there was more stability of measures among those who only ingested the treatment medication.

In this preliminary evaluation of the method, \( p \) values below 0.1 are noted. This extended level of statistical acceptance is appropriate for this initial proof of concept evaluation.
RESULTS

Fault analyses

As shown in Table 1, the overall success rate was very high; that is, nearly every time a subject attempted a trial they were eventually successful. The success rate (percentage obtaining a successful sequence on the first attempt of each study day) in participants after minimal experience (2 weeks or about 6 exposures) was 72%, and if the four participants who had trouble obtaining stability were eliminated, the overall success rate was further increased. Thus, even when patients are maintained on methadone (6), or buprenorphine (7, 8), drugs known to produce miosis, reliable pupillary measures were obtained.

Shown in Table 2 are the mean and standard deviation of the four parameters collected on subjects (n = 6) on days when their urine was negative for drugs of abuse (minimum of 10) compared with days when their urine was positive for abused drugs. Although the mean values are similar, the variability increased (larger standard deviation) for ID, CL and SV on urine-positive days. The variability in the measures obtained for constriction amplitude was similar regardless of the presence of illicit drugs in the urine.

Many of the participants were never able to provide ten or more drug-free urine samples (n = 20) and a few always gave urine samples that were drug-negative (n = 4). The data from these subjects were not useful for the comparisons illustrated in Table 2, but examination of the variation of the parameters in Table 3 reveals a similar pattern: that the standard deviation of the mean of ID, SV and CL was larger in the group that had the positive urine samples.

Participants with 10 or more clean days were analyzed using the FIT equation. A baseline was established from pupillary data on days when the urine was negative for illicit drugs. The pupillary measures from days when the urine was positive for abused drugs were inserted into the FIT equation to determine whether deviations merited detection (p = 0.1 to p = 0.01). For example, participant LH had baseline values of 5.35 (± 0.68), 0.97 (± 0.12), 281.52 (± 8.0) and 78.2 (± 9.8) for ID, CA, CL and SV, respectively. On a day when the urine was positive for cocaine and amphetamine, the values for the four parameters were 6.31, 0.79, 305.1 and 91.23. When inserted into the equation this generated a FIT index of 14.69, a value well above the critical values for the

| Overall success rates for attempts (%) | 92.9 |
| First attempt success (after 3 exposures) (%) | 72.0 |
| First attempt success after elimination of 4 participants (%) | 81.0 |
| Overall first attempt success (%) | 58.9 |

TABLE 1. Analysis of successful pupillometry by participants (n = 37); total attempts = 2370.

DISCUSSION

The effects of various classes of psychopharmacologic drugs on the size of the pupil, its response to a flash of light (light reflex) and to the ability to track moving targets (smooth pursuit or saccadic movement) are widely known (10). Although acute effects of drug administration have been documented, there are no studies on the pupillary effects of concomitantly administered drugs. This is an especially important deficiency because current drug abuse patterns suggest the predominance of poly-drug use (11). In the present study, an instrument that has proven useful in evaluations of fitness for duty (12) was used in participants enrolled in an opiate treatment protocol. Although the participants were given only a single introduction and short training session with limited practice, most subjects successfully learned to use the instrument efficiently. Overall, 93% of the attempts to use the instrument were successful. Many of the failures were attributed to four participants who were unable to achieve consistent performance. In workplace applications, where there is less drug use and more conventional nutrition, sleep habits and lifestyle, the instrument works consistently well in 99% of the subjects overall and 85% are successful on the first attempt (PMI documents, unpublished results). Participants were main-
tained on methadone (6) or buprenorphine (7, 8), drugs known to cause miosis. In a previous study (13) with another automated pupillometer, small pupillary diameter was a methodological problem that was not encountered with the PMI instrument. Also, participants with dark colored irises were a challenge when using other pupillometers but they did not seem to affect the performance of the instrument used in this study.

The ability of the instrument to detect concomitant drug use rests on the change from an individually determined stable baseline accumulated over drug-free days. Several readings are obtained to determine an average pupillary measure (e.g., ID) and the variations that ordinarily occur. The results of any given test are compared with the stored baseline data for the subject. Detection becomes more sensitive as the baseline deviation becomes smaller. In workplace applications sensitivity is enhanced by repeated testing; a procedure that diminishes the standard deviation of each pupillary parameter. Baselines are initially developed with 10 test points, although analyses of actual study data indicate that 25 data points is the ideal minimum number data points for the Goodness-of-Fit calculation with 4 degrees of freedom. Therefore the FIT system continues to develop the baseline over time to improve its sensitivity. As baseline physiologic changes occur, the rolling baseline calculation maintains the most recent normal condition (PMI internal documentation).

In the present study, some evidence supported the notion that a similar strategy could be used in the drug treatment clinic. The variability of all four (ID, CA, CL, SV) of the measures was higher when the participants had drug-positive urines than when the urine was drug-free. Likewise, in the few subjects that always presented with drug-negative urine (n = 4), the standard deviation of the pupillary measures was smaller than subjects that always presented with drug-positive urine (n = 20).

Potential problems with the evaluation of the instrument in a clinical treatment program must be acknowledged. Our participants very frequently used drugs (legal and illicit) other than the treatment medication, making it difficult to obtain a stable baseline. Specifically, the baseline standard deviations for subjects (n = 6) was substantially larger than those reported in a nontreatment population: (ID 0.51 vs. 0.17; CA 0.12 vs. 0.06; CL 12.1 vs. 7.5; SV 7.2 vs. 7.0) (PMI unpublished results). The OnTrak Teststk used to detect illicit drugs is generally reliable (14), but there have been reports of errors in some applications (15). Furthermore, the urine tests were qualitative and detected recent drug use. Both dose and time after administration are known to influence the pupillary effects of drugs (2, 3) and these were uncontrolled and unable to be measured in this study. Thus, we were unable to parametrically evaluate a drug interaction. However, we were able to determine that concomitant drug use in opioid-maintained patients increased the variability in pupillary measures when compared with their own-drug free days or when considered as a group.

Our preliminary evaluation emphasizes the need to further develop automated pupillometry for the study of drug interactions and mechanisms for drug-induced changes in pupillary parameters. Refinements of the method might include consideration of pupillary area rather than diameter. Pong et al. (16) found that pupillary area was more sensitive than diameter in measuring changes in the light reflex in Macaque monkeys. In probation, parole and drug court populations, weighting factors that emphasize CA and CL, over other pupillary measures were more predictive of drug ingestion than algorithms that used all four parameters with equal weighting. (Crucilla, C., PassPoint, Inc, unpublished documents). Clearly refinements in the methodology are needed. We reported results with significance levels below 0.1 in this preliminary evaluation; further specificity would be necessary to increase the accuracy for drug-detection applications.

Eventually, pupillometry readings may be used to make accurate conclusions about the current toxicity status of opioid-maintained or other chronically-treated patient populations. The clinical context of the present evaluation represents both a strength and weakness of the design. From a practical perspective, a strength of the study rests in its real world application. Our evaluation qualitatively indicated that concurrent drug use may be detected by pupillary measures. Pupillometry methods may eventually offer an alternative to costly, inconvenient and easily defrauded urinary screening (17-19).

REFERENCES

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