Clinical pain research

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Dynamic assessment of the pupillary reflex in patients on high-dose opioids

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Abstract

Background and aims: Pupil size and reaction are influenced by opioids, an effect that is not considered to be affected by opioid tolerance. As clinicians have observed patients on high-dose opioids who exhibited seemingly normal pupil sizes, we wanted to dynamically assess the pupillary reflex in cancer patients on high-dose opioids.

Methods: We performed a dynamic assessment of the pupillary reflex in cancer patients on high-dose opioids and a control group of healthy volunteers using a portable, monocular, infrared pupillometer. We also performed a clinical examination and measured blood concentrations of opioids and their active metabolites.

Results: Sixty three patients who were on opioids for 2 months (median time) and on an oral morphine equivalent dose of 250 mg (median dose) were investigated. Most patients used more than one opioid. When correcting for age, pupil size in the group that had received no increase of opioid dose over the last 14 days was not significantly different from pupil size in the healthy volunteer group ($p=0.76$), while the group that had increased the dose of opioids differed significantly from healthy volunteers ($p=0.006$). We found no statistically significant correlation between total oral morphine equivalents and pupillary reactions or between blood opioid or opioid metabolite concentrations and baseline pupillary changes.

Conclusion: Pupillary changes do take place in patients on opioids. However, tolerance to these changes occurs when

medication is not increased over time. Dynamic pupillometry can give additional information about the degree of tolerance to opioids.

Implications: These findings elucidate previous misconceptions regarding pupillary effects and tolerance to opioids.

Keywords: opioids; pain; pupillary reactions; tolerance.

1 Introduction

Pupil size reflects the balance between sympathetic and parasympathetic nervous systems. Pupil size and reaction are also influenced by drugs. Opioids generally cause pupillary constriction (miosis), which is not affected by opioid tolerance according to the literature [1–9]. However, some claim that tolerance to the miotic effects of opioid agonists exists [10–13]. Clinicians treating cancer patients on high-dose opioids have also noticed that a few patients on high-dose opioids do not always present with small pupil size [14].

We wanted to perform a dynamic assessment of the pupillary reflex in patients on high-dose opioids. In addition to pupil size measurements under standard room light conditions, the pupillary light reflex was assessed when the pupil was exposed to a standard light stimulus. We also determined pain intensity, sedation score, and other side effects of opioids, and we measured blood concentrations of opioids and their active metabolites.

The aims of the study were to monitor the dose and time effects of opioids on pupil size and pupillary reactions in patients using opioids. Furthermore, we wanted to compare dynamic pupillary reactions with doses and blood concentrations of these opioids and their active metabolites.

2 Methods

The study was approved by Regional committee for Medical Research Ethics in Eastern Norway (REK No. 420-07197a 1.2007.1165) and Social Science Data Services

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at Oslo University Hospital (NO. 849). Written informed consent was obtained from all subjects.

Cancer patients (in-patients and out-patients) who had been referred to the Pain Section at the Norwegian Radium Hospital were recruited. Patients who had used opioids for a minimum period of 4 weeks and with an opioid dose corresponding to at least an oral morphine equivalent dose of 60 mg per day were included. The conversion table used was from the New York City Department of Health and Mental Hygiene [15]. The following patients were excluded: (1) patients who had undergone eye surgery that may influence pupillary reflexes, (2) patients on local medication that may influence pupillary reflexes, (3) patients with amyloidosis, multiple sclerosis, Horner's syndrome, or ongoing migraine attacks, and (4) patients with a brain tumour.

Dynamic pupillometry was performed with a portable, monocular, infrared pupillometer, AlgiScan™ (Idmed, Hôtel Technoptic, 13013 Marseille, France). While patients were sitting on a chair in a room with standard lighting, a silicon positioning eyecup attached to the AlgiScan™ camera was placed over one eye to block out all external light, and an eye-pad was placed on the other eye. AlgiScan™ is an infrared video pupillometer used to measure the pupil diameter. In addition, AlgiScan™ measures the dynamic pupillary light reflex generated by photo-stimulation.

The AlgiScan™ provides accurate and reproducible measurements of the pupil diameter as well as of the characteristics of its dynamic evolution: baseline pupillary diameter, percentage decrease in size after a standardised light stimulus (variation), time before contraction starts (latency), and speed of evolution (velocity).

Through interviews and clinical examinations we also determined the following variables:

- Edmonton Symptom Assessment System (ESAS) [16], which includes assessment of pain, fatigue, sedation, nausea, and constipation using an 11-point NRS scale (Numeric Rating Scale)
- Cognitive function based on a subjective evaluation after conversation with the patient (11-point NRS scale)
- Use of opioid analgesics (total dose expressed in corresponding morphine equivalents, type of opioid, form of administration)
- Automobile driving (Yes/No) daylight and automobile driving (Yes/No) at night.

In addition, blood samples were analysed for morphine and its metabolites [morphine-3-glucuronide (M3G), morphine 6-glucuronide (M6G)], oxycodone, buprenorphine,

fentanyl, and methadone. Measurements were performed at the Department of Forensic Sciences, Oslo University Hospital, using routine, validated, forensic chromatographic methods. Quantitative analyses of morphine, M3G, M6G and oxycodone were performed using ultra high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) [17, 18]. Buprenorphine and fentanyl were quantified using a previously published UHPLC-MS/MS method [19]. Methadone was quantified by a fully validated method that uses a sample preparation procedure and UHPLC-MS/MS conditions similar to the one used to measure buprenorphine [18]. Blood samples were drawn shortly after the clinical examination and the pupillometry measurements.

The patients included in the study were divided into two groups when analysed for dynamic pupillary reactions, depending on whether their opioid-dose was increased during the last 14 days or not (Increase group and No-increase group).

We also performed a control study on 20 healthy volunteers who were not using opioids before the start of the study in order to obtain baseline values in persons not taking opioids.

3 Statistics

A sample size estimate based on earlier studies was not performed as there is no documentation of a minimum number of patients needed to obtain statistically meaningful data on the variables of interest. However, we considered 60 patients to be sufficient to explore our research questions.

Descriptive statistics are presented for demographic data and clinical characteristics. Patient characteristics (including ESAS registration) and opioid concentration with metabolites are reported with median, quartiles and range. Dynamic pupillary reactions are reported with mean and standard deviation.

A possible association between the dynamic pupillary changes and total opioid doses was investigated with Pearson Product-Moment Correlation. The same statistical method was used to explore possible associations between dynamic pupillary changes and blood concentrations of the different opioids and their metabolites. Pearson Product-Moment Correlation was also used to test for relationship between age and baseline pupil size.

One-way ANOVA was used to compare the three groups (Increase group, No-increase and Volunteers) regarding differences in the dynamic pupillary reactions.

Analysis of covariance (ANCOVA) was used to compare the patient data with volunteer data when correcting for age differences. $p \leq 0.05$ was considered significant.

IBM SPSS (version 22; IBM SPSS, Armonk, NY: IBM Corp.) was used for statistical analyses. Sample characteristics are presented as the median with 25th and 75th percentiles in parenthesis, in addition to range.

4 Results

We investigated 63 patients (25 men and 38 female) and 20 healthy volunteers (nine men and 11 female). Patient characteristics were recorded, as well as time on opioids, opioid dose, and blood concentrations of opioids and their metabolites (Tables 1 and 2). For the 20 healthy volunteers, the median age was 55 years (34, 61), range 23–68.

Table 1: Age and ESAS score of patients.

	Median	25th and 75th Percentiles	Range	No.
Age of patients	61	53, 69	22–86	63
Cognition	0	0, 0	0–4	58
Pain	4	2, 5.25	0–10	62
Tiredness	5	3, 6	0–10	62
Drowsiness	4	3, 6	0–10	62
Nausea	0	0, 3	0–10	62
Lack of appetite	3	0.75, 6	0–10	62
Shortness breath	2	0, 5	0–10	62
Well-being	5	2, 5	0–10	59
Constipation	4	0, 6	0–10	62

ESAS score (Edmonton Symptom Assessment system) at consultation. Cognition, pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, well-being, and constipation are represented as a number on an 11-point numeric rating scale, where 10 is the maximum and zero is the minimum. No. = number of patients.

Table 2: Opioid dose and blood concentrations.

	Median	25th and 75th Percentiles	Range	No.
Time on opioids	2 months	1, 7	1–300	63
Morphine equivalents	250 mg	150, 370	50–840	63
Morphine	0.128 $\mu\text{mol L}^{-1}$	0.066, 0.243	0.031–0.992	18
M3G	1.246 $\mu\text{mol L}^{-1}$	0.225, 2.864	0.071–4.330	25
M6G	0.310 $\mu\text{mol L}^{-1}$	0.166, 0.966	0.056–1.605	18
Oxycodone	0.261 $\mu\text{mol L}^{-1}$	0.155, 0.577	0.050–1.218	41
Fentanyl	0.004 $\mu\text{mol L}^{-1}$	0.002, 0.005	0.002–0.012	9
Methadone	0.366 $\mu\text{mol L}^{-1}$	0.158, 0.673	0.066–1.403	8

Morphine equivalents: all opioids converted to oral morphine equivalents in mg. No. = number of subjects with the drug detected in blood (above the analytical cut-off level).

In the patients, the median oral morphine equivalent dose was 250 mg. The median time on opioids was 2 months (Table 2). Several patients used more than one opioid: 16 patients were on two different opioids, seven patients on three different opioids, and one patient on four different opioids. Oxycodone was the most frequently used opioid (45 patients), while 21 patients used morphine, 12 patients used transdermal fentanyl, and nine patients used methadone, according to self-report and medical records. Administration of opioids also varied: 60 patients used oral medication, 12 patients used transdermal administration, five patients received subcutaneous infusions, five patients had intravenous infusions, one patient had a spinal administration, and one patient had a transnasal application. Measurement of blood drug concentrations confirmed the self-reported use of drugs in most subjects, with small deviations in single drug detections. Details in number of positive blood samples and drug concentrations are seen in Table 2. Twenty-three patients received constant amounts of medication with no increase in opioids over the last 14 days while 38 patients had an increase in opioid dose over the last 2 weeks (missing data on two patients regarding increase in opioid dose).

We found no statistically significant correlation between total oral morphine equivalents and baseline pupil size ($r = -0.237$, $n = 59$, $p = 0.070$), variation after light stimulus ($r = -0.247$, $n = 59$, $p = 0.057$), velocity of response ($r = -0.220$, $n = 58$, $p = 0.098$) or latency of response ($r = 0.100$, $n = 58$, $p = 0.453$). Furthermore, we found no statistical correlation between blood concentrations of any opioid metabolites and changes from pupil size, variation, velocity, or latency.

There was a statistically significant difference between the three group (Increase, No-increase, volunteers) regarding baseline pupil size as determined by one-way ANOVA [$F(2,75) = 32.53$, $p = 0.000$]. A Tukey *post hoc* test revealed

that the baseline pupil diameter was significantly smaller in the Increase group (3.71 ± 0.79 mm) compared to the No-increase group (4.73 ± 0.79 mm, $p=0.008$), and the No-increase group baseline pupil diameter significantly lower compared to volunteers (5.51 ± 0.89 mm, $p=0.000$), see also Table 3.

Also, a corresponding significant difference as determined by one-way ANOVA in variation [$F(2,75)=8.1$, $p=0.001$] and velocity [$F(2,73)=32.11$, $p=0.000$], but not

Table 3: Results of dynamic pupillometry in patients using opioids and healthy volunteers not using opioid medications.

Patients and volunteers	Baseline (mm)	Variation (%)	Velocity (mm s^{-1})	Latency (ms)
Increase group				
No	36	36	34	35
Mean	3.71	30.9	3.01	276
Std. deviation	0.79	7.0	0.82	242
No-increase-group				
No	22	22	22	22
Mean	4.73	35.9	3.89	243
Std. deviation	0.79218	8.0	0.94	44
Healthy volunteers				
No	20	20	20	20
Mean	5.5	40.2	5.12	237
Std. deviation	0.89	10.8	1.09	32

Baseline = pupil size before stimulation; variation = decrease in pupil size after stimulation; velocity = speed of pupillary contraction after stimulation; latency = time before contraction starts.

in latency [$F(2,74)=0.44$, $p=0.64$] was seen between the three groups, see also Table 3.

As we found a strong correlation between age and baseline pupil size in healthy volunteers ($r=-0.776$, $n=20$, $p=0.000$), we performed an analysis with age as a covariate. When correcting for age, pupil size in the group with no increase in opioid dose over the last 14 days was not significantly different from pupil size in healthy volunteers [$F(1,39)=3.32$, $p=0.076$]. See also Fig. 1. The Increase group still differed from healthy volunteers, when corrected for age ($p=0.006$).

Eleven patients on opioids drove a vehicle and had a baseline pupil size of 4.1 mm (3.3, 4.5) and a velocity of 3.18 mm s^{-1} (2.2, 2.79). Six of the patients had an increase in opioids over the last 2 weeks. Five patients also drove a vehicle at night, and had a baseline pupil size of 3.4 mm (2.97, 4.97). Three of these patients had an increase in opioids over the last 2 weeks.

Ten of the 23 patients with no increase in opioids had no constipation, and seven of these patients did not use laxatives.

5 Discussion

We found that several changes in pupillary reactions – not only in pupil size – occur in patients on opioid medication. In contrast to what has been claimed in many publications, we

Fig. 1: Relation between age and baseline pupil size in patients using opioids (but without increase in doses the last 14 days) and healthy volunteers with no opioid medication. Red dots = patients with no increase in opioids. Blue dots = healthy volunteers.

found that tolerance to miosis takes place in some patients who are on a stable opioid dose. Although there was a tendency to smaller pupil diameter and a less variation in pupil size after a light stimulus in patients on higher total opioid dose, there was no statistical significant correlation seen between opioid dose and pupillary reactions, or between opioid blood concentrations and baseline pupil size. This indicates that tolerance has developed, rendering drug dose and concentrations less relevant for changes in pupillary reactions. These findings are supported by the covariate analysis demonstrating the non-significant baseline pupil size in patients who had not increased their opioid dose over the last 2 weeks compared to healthy volunteers not using opioids, when using age as a covariate, since age also influences pupil size. In Fig. 1, this is illustrated by showing a number of patients taking opioids that actually have larger baseline pupil diameter compared to healthy volunteers. The non-correlation between opioid dose (based on oral morphine equivalents) and baseline pupil size ($p=0.070$) should be interpreted with caution as the accuracy of different equivalence tables could be questioned [20, 21].

Pupillary changes are complicated and reflect a balance between the sympathetic and the parasympathetic nervous systems in which numerous neurotransmitters are involved [22–24].

Miosis due to opioids is caused by stimulation of the Edinger–Westphal nucleus pathway in the brain stem [22]. However, in patients who use high-dose opioids, excitatory effects are caused by different mechanisms. It is not clear whether these effects also can influence miotic constriction [5]. Dynamic changes in pupillary reactions also take place during opioid withdrawal, even when methadone is given as a substitute drug [11, 25].

Many earlier studies on opioid-induced pupillary changes were performed in animals. The effect of opioids on the pupillary light reflex in animals and humans has been studied previously with inconclusive results. In cats and dogs, opioids depress the light reflex [26, 27], whereas in rabbits, the light reflex is enhanced [28]. In anesthetized humans, the light reflex is not depressed after alfentanil (opioid) administration with controlled ventilation [29], but the effects of the combination of opioids and significant sympathetic nervous activation, induced by respiratory depression, were previously uncertain [30].

Furthermore, most measurements of pupillary size and reactions were static measurements in the past [23, 24, 31, 32]. We believe that a dynamic video pupilometer, which measures amplitude changes after a light stimulus under standard conditions, provides additional information about chronic opioid use and pupillary reactions. Others have shown an effect of age on the pupillary light

reflex [30, 33]. This is in agreement with our results. Therefore, when evaluating pupil size and pupillary reactions, the patient's age should be taken into consideration. We found a significant change in pupil size and reactions even in patients on a stable dose of opioid(s) compared with healthy volunteers. However, when the variables were corrected for age, the difference was not significant. This is in accordance with our clinical observations that some cancer patients on high-dose opioids, over time, do not present with the typical constricted pupils, as would be expected. It seems that tolerance to pupillary reactions due to opioids develops in these patients. When the opioid dose escalates the usual dose, pupils constrict again, and, at this moment, these patients will possibly also experience over-sedation and respiratory depression.

It is interesting that while changes in patients on opioids do take place in baseline pupil size and velocity of contraction after a light stimulus, the latency before contraction starts seems to be unchanged. The variation (% contraction) probably reflects the reduced pupil size before contraction starts.

Many patients using opioid medication on a regular basis have been advised not to drive out of concern that these drugs influence perception, cognition, and coordination [34]. However, as tolerance to many of these effects develops, the decision to allow a patient to drive an automobile is often made on an individual basis [35]. In our opinion, pupil size and pupillary reactions could be part of this assessment as they directly influence the patient's perception and coordination when driving an automobile, especially, at night.

Since 10 of the 23 patients with no increase in opioids had no constipation, and seven of these patients did not use laxatives, we speculate that tolerance to opioid-induced constipation also occurs in some patients.

There are several limitations in this study that should be acknowledged. Opioid drug blood concentrations were not measured at steady state, but patients were tested at a convenient time without considering the time of drug intake or the half-life of the opioids. Furthermore, many patients were on several opioids with different pharmacokinetic and pharmacodynamics effects. If there are differences in pupillary responses related to different opioids or opioid metabolites, a study of patients taking one opioid at a time and measuring drugs at steady state may be necessary. There are, however, reasons to believe that all μ -receptor agonists will have similar effects on pupillary changes, but the affinity for the μ -opioid receptor of different drugs may also play a role.

When opioid doses are decreased, even when the time since last dose is prolonged, withdrawal reactions could

occur. Withdrawal reactions will often result in mydriasis [36, 37]. All our patients were either on stable doses of opioids or had their doses increase during the last 2 weeks. None of the patients presented themselves with the typical withdrawal symptoms like sweating, tremor, restlessness, irritability, gooseflesh skin, or tearing. The fact that the prescribed opioids mostly were detected in blood also support that withdrawal was not pronounced.

6 Conclusion

Pupillary size, degree of contraction, and speed of contraction due to a light stimulus are all dynamic changes that take place in patients using opioid medication. Tolerance to these changes occurs when pain is stable and medication is not altered. When the opioid dose escalates above the usual dose, pupils constrict again once more. Dynamic pupillometry can give additional information about the degree of tolerance to opioids, which could, among other data, be useful when discussing whether to permit the patient to drive a vehicle while taking opioid medication.

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Authors' statements

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