The opiate addiction test: a clinical evaluation of a quick test for physical dependence on opiate drugs

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1 Mydriasis (pupil dilation) in response to conjunctivally applied naloxone hydrochloride has been demonstrated using an innovative electronic binocular pupillometer in 40 opiate dependent patients, on maintenance methadone treatment.

2 No pupillary response to naloxone was seen when an identical procedure was carried out in a control population of 12 healthy volunteers.

3 After a baseline measurement of pupil size, two drops of naloxone hydrochloride were instilled into the conjunctival sac of one eye. Serial binocular pupillometry was then carried out at 5, 10, 15, 20, 25, 30, 35, 40 and 45 min post-instillation.

4 Discriminant analysis between the control and patient groups showed that the false negative rate (error of misclassification to the wrong population) was lowest (20%) at 40 min post-eyedrop instillation, with no false positives in the control group.

5 The study has therefore shown an improvement in the previously reported false negative rate (25%) [1, 2], of the conjunctival naloxone test of opiate dependence, with the use of our innovative electronic binocular pupillometer.

Keywords  opiate addiction  naloxone  pupil  pupillometry  ophthalmic solution

Introduction

Opiate drugs and their derivatives are well known to bring about pupil constriction (miosis) in man. It is thought that this is due to a central action, either by direct stimulation of the Edinger-Westphal Nucleus (EWN) [3, 4] or by depressing the cortical centres responsible for inhibition of the EWN [5]. The possibility that the miotic action of opiates could be a result of a local effect in the iris has also been investigated [6, 7].

Significant mydriasis in response to topically applied naloxone solution has been demonstrated in previous studies carried out in this department [1, 2]. In these studies pupil sizes were measured with a polaroid camera system before eyedrop instillation, and at 30 min and 45 min after eyedrop instillation (also at 60 min in [1]).

Both of these studies reported no mydriasis in approximately 25% of known opiate dependent subjects. We postulated that some of this false negative rate may be due to suboptimal measurement and therefore, an innovative electronic binocular pupillometer has been used in the current study. Also, time of measurement relative to naloxone administration, and ambient light levels may be factors in determining the sensitivity of the test. The current study measures the time course of the mydriasis by making measurements of the drug induced anisocoria (difference in size between the right and left pupil) in both opiate-dependent patients and control subjects every 5 min for a period of 45 min post-naloxone administration to determine the optimum time (average time to peak response) for pupil size measurement, and at three light levels for each time point.

Methods

Patients

Ethical approval for the study was obtained from the Wandsworth Health Authority Ethics Committee, and all subjects gave written, informed consent prior to entry into the study. The patients were recruited consecutively from those attending our Centre for Addiction Studies who fulfilled the inclusion criteria; all
patients were aged between 18 and 60 years, free from any neurological or ophthalmic disease and receiving a maintenance dose of methadone. 

The effect of conjunctival naloxone on pupil size was investigated in 40 opiate dependent patients (27 M, 13 F), mean age 35.1 years (age range 20–59 years); all patients were receiving a maintenance dose of methadone of between 10 mg and 150 mg day\(^{-1}\) (mean dose 45 mg day\(^{-1}\)). Four of the opiate addicts were receiving other prescribed drugs (disulfiram (Antabuse); amitriptyline; diazepam and carbamazepine (Tegretol); and carbamazepine (Tegretol) respectively). All the patients gave routine urine samples for toxicological analysis. Eight patients were using other illicit drugs at the time of the test (amphetamines (1), morphine (5), cannabis (1), codeine (1) and benzodiazepines (4)). All patients were questioned for recent past illicit drug abuse, duration of opiate abuse (mean 14.4 years; range 1–40 years), time elapsed since last dose of methadone (mean 9 h, range 1–27 h), and size of last methadone dose (mean 31.5 mg, range 5–60 mg).

For comparison, variation in anisocoria in the normal population was measured in 12 healthy volunteers (8 M, 4 F), all employees of St George's Hospital. None of the subjects was using any medication at the time of the test.

Pupillometry

Patients were seated in a room with an average illumination of 40 lux (produced by directing a desk lamp fitted with a 60 W bulb at a light coloured wall) for the entire assessment period.

After a 5 min adaptation period to the room's lighting conditions a pupillometric measurement was made using our electronic binocular pupillometer. The binocular instrument, which is capable of measuring pupil size with \(\pm 0.1\) mm precision and offers measurements with 2% variability, houses twin objective lenses coupled to a two dimensional infrared sensitive CCD array. Provision for infrared illumination, as well as controlled illumination and accommodation for the subject is within the instrument 'head'. A tungsten bulb behind a diffusing plate was able to give three discrete light levels of 60 lux, 230 lux and 700 lux, corresponding respectively to: a dimly lit room, a well lit room and bright outside daylight.

Two drops of 0.1% w/v naloxone hydrochloride solution were then instilled into the conjunctival sac of the right eye. The naloxone eyedrops (St George's Eyedrop Formulation) were factory prepared in sterile single dose sealed plastic dropper pipettes and opened immediately before instillation.

Pupillometric measurements at each light level were then made every 5 min up to 45 min post-instillation. This period was chosen on the grounds of estimated peak response time and subject compliance.

Many people show a degree of anisocoria, so measurement of its change relies upon a correction for any initial inequality in pupil size. Measurements using this pupillometer show that fractional anisocoria, defined as the ratio of pupil difference to mean radius, is approximately constant in an individual over a range of pupil diameters. We have therefore used changes in fractional anisocoria over the recording period as a measure of the effect of naloxone instillation on pupil size.

Using the statistical package SAS [8], a discriminant analysis [9] was used to determine which of the three light levels was best for distinguishing between the control and patient groups and at which time point post-naloxone instillation the probability of misclassification was minimal. (The 'within' covariances were used in the calculation of the discriminant functions as the two groups did not have equal covariance matrices).

The estimated error rate or probability of misclassification may be optimistic when using the same people to create and then assess the discriminant function. The 'leaving one out' method of crossvalidation gives a more realistic view as each person in turn is left out of the dataset used to create the discriminant function but then assessed by the function [10].

Results

All patients and normal subjects recruited completed the study. Of the three light levels investigated (60, 230, 700 lux), light level two (230 lux) was found to give the greatest probability of the correct classification of individuals. Taking all measurements (\(n = 468\)) made at light level two, 64% of patients were correctly classified and 89% of control subjects were correctly classified.

Having identified light level two as optimal, all measurements made at this light level were used to determine at which time point post-instillation the greatest number of individuals were correctly classified to the right population. Figure 1 shows the mean (± s.e. mean) fractional anisocoria for the opioid dependent patients and control subjects at each time point at light level 2. Time point 8 (40 min post-instillation) was found to give the smallest number of misclassifications, at this time point 80% of the patients and 100% of the control subjects were correctly classified. Using crossvalidation 77% of the patients and 100% of the control subjects were correctly classified.

In determining a time range in which the post-naloxone instillation pupillometric measurement

![Figure 1](image-url)

**Figure 1** Mean (± s.e. mean) fractional anisocoria for the opioid dependent patients and control subjects at each time point at light level 2 (230 lux).
should be made in a clinical situation, the time range 35–45 min post-naloxone instillation was found to yield the smallest error rates. If the post-naloxone pupillometric measurement is recorded between 35 and 45 min post-instillation 76% of the patients and 94% of the control subjects are likely to be correctly classified, this is borne out using crossvalidation.

Discussion

Detection of opium and its metabolites in urine or blood is not proof of opiate dependence. A subject wishing to gain access to methadone via a Drug Dependency Treatment Program can add drugs to urine, obtain a specimen from somebody else, or take a single dose to give a positive result. Development of a reliable and accurate method of detecting subjects who are physically dependent on opiate drugs is important to allow doctors, community drug teams and specialist centres to prescribe methadone promptly to those patients who need it.

All opiates induce pupillary constriction whether the individual is physically dependent on them or not. The mydriasis following the instillation of naloxone eyedrops in opiate dependent individuals has been previously demonstrated [1, 2]. Naloxone does not produce mydriasis in subjects who have not received an opiate [1] or in subjects who have received an opiate but who are not physically dependent [2]. In the previous reported studies approximately 25% false negative responses (known opiate dependent subjects who showed no naloxone induced mydriasis) were noticed.

In an attempt to identify the time and conditions of maximal pupil response with the aim of reducing the false negative rate, the current study was designed to investigate the time course of the naloxone induced mydriasis in opiate dependent individuals and the optimum ambient illumination level for pupillometric assessment. The electronic binocular pupillometer used in the current study has increased spatial accuracy and provides a more controlled measurement environment than the pupillometer used in previous studies.

Patients newly presenting to a Drug Dependency Clinic take part in Standard Assessment Procedures, it is therefore important to understand how the Opiate Addiction Test can be incorporated into this assessment, bearing in mind the 40 min time frame of the test. If an error of ±5 min is made with respect to the 40 min post-naloxone instillation measurement (i.e. the measurement is made 35–45 min post-instillation), the chance of determining physical opiate dependence in dependent subjects is reduced from 80% to 76%, likewise, the chance of correctly determining the status of a non-dependent subject is reduced from 100% to 94%. Therefore at present, accurate post-instillation timing is critical.

Using the measurement conditions and methods described in this study, the number of false negative results has been reduced from the 25% reported in previous studies carried out in this department [1, 2] to 20%, indicating the necessity of precision pupillometry and critical timing of the pupillometric measurements in determining opiate dependent individuals from a random population of subjects. The Opiate Addiction Test is currently being used in our Drug Dependency Unit to validate these findings, and to attempt to increase the sensitivity of the test still further.

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