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Static and Dynamic Pupillometry for Determination of the Course of Gradual Detoxification of Opiate-addicted Patients

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Summary. In order to assess the course of methadone (Heptadone) substitution therapy, 29 inpatients at the Vienna Psychiatric University Clinic (21 males, mean age = 27 years, SD 4 years; 8 females, mean age 29.75 years, SD 5.28 years) who were addicted to opium tea or to a mixture of opium and heroin were investigated by means of computer-assisted "static"- and "light-evoked dynamic" pupillometry. Pupillary measurements were carried out before the start of withdrawal, on the 2nd day 48 h after the administration of 10 mg methadone, and again after the maximum and half of the maximum dose of methadone had been administered. The constricted pupils (the effect of opiate) showed dilatation after the withdrawal syndrome appeared, but immediately after the start of the detoxification treatment, as well as 1 day after administration of the maximum methadone dose a decrease of pupillary diameter was observed. The narrowing of the pupil was followed by an increase in pupillary diameter, which peaked 48 h after the last minimal dose of methadone and nearly reached the normal level. The widening of the pupil reflects an increase of noradrenergic activity under conditions of opiate withdrawal. An increase of spontaneous fluctuations was observed during withdrawal and was only inhibited by the maximum dose of methadone. Finally, pupillary dynamics (shortening of latency time and increase of relative changes) improved during therapy. The pupillary measurement coresponded with clinical observations as well as with self-evaluation during treatment. Thus pupillometry seems to be a useful instrument for assessment of treatment of opiate-addicted patients.

Key words: "Static" pupillometry – "Dynamic" pupillometry – Opiate – Withdrawal syndrome – Methadone

Introduction

In stopping or reducing the dose in opiate-addicted patients a typical withdrawal syndrome lasting about 3–5 days and producing particular complaints can be observed (Kolb and Himmelsbach 1938). It is characterized by a feeling of restlessness, weakness, aching bones and muscles, dysphoric and even depressed mood, increased psychomotor activity and a loss of appetite, nausea, vomiting, diarrhoea and other vegetative symptoms, such as increased sweating, tachycardia, a rise in blood pressure, etc. Another vegetative sign is the widening of the pupil which had been constricted by previous intake of opiates. However, the extent of complaints is related to constitutional and circumstantial factors. In order to avoid an unnecessarily prolonged treatment, on the one hand, and to supply an efficient dose of the substitute medication, on the other, it is desirable to be able to measure the degree of vegetative symptoms. As the pupillary diameter decreased under the influence of opiates increases after withdrawal of the drug, the measuring of changes in the size of the pupils can be used for determinating the course of detoxification.

As advances in modern electronic technology have recently improved recording and evaluation techniques, it has become possible to measure pupillary diameter and reaction more objectively, economically and accurately than previously. In addition, repeated measurements can be performed without discomfort of the patients (Grünberger et al.1984a–c). Computer-assisted measuring of the pupillary diameter (static pupillometry) as well as the pupillary reaction to a light stimulus (light-evoked dynamic pupillometry) has been carried out in both psychopathological and psychopharmacological research. The high reliability of the static variability of pupillometry has been confirmed. Variables measured during static and dynamic pupillometry have been factor-analysed. Four factors were obtained regardless whether investigation were carried out in healthy normals or in psychiatric patients (Grünberger et al. 1978b).

Subjects and Methods

Twenty-nine patients (21 male, 8 female) were subjected to an inpatient detoxification treatment with methadone (Heptadone) in

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the intensive care unit of the Psychiatric University Clinic of Vienna. The average age of the male patients was 27.4 years (SD 4), of the female patients 29.7 years (SD 5.28), (total mean 28; SD 4.42). Twenty-two of them had taken opium tea, which is an extract of dried poppy heads. Seven had consumed the mixture of opium and heroine before they were taken into hospital. None of the patients had taken any sedative substances within the preceding 2 weeks. Urine samples obtained to assess the detoxification process were analysed for illegal drugs by menas of Emit-DAO every day.

Pupillometry. The examination of the patients was carried out with a microprocessor-assisted T.V. pupillometer 1050 developed by the Whittaker Corporation. The measurements were performed in a sound attenuated room with a constant illumination of 160 lx. The methodology of static and light-evoked dynamic pupillometry has already been described (Grünberger et al. 1984b, c). Furthermore self-evaluation by means of a self-rating scale (FEO) (Loimer et al. 1988) was carried out.

Design of Investigation. For the determination of the initial fixed dose of mehadone the patients had to be free of drugs for 24 h. At the beginning of the trial 10 mg methadone (Heptadone) was administered. Subsequently, the patients were given a 5-mg dose when they asked of it until the complaints caused by withdrawal were sufficiently suppressed. During the following days the methadone dose was reduced step by step, trying to decrease medication by 20% in comparison the day before. In some patients, however, the dosage was either kept the same or reduced by less than 20%. The pupillometric investigations and the self-evaluation were carried out at the following times: The first examination was accomplished before the patients were taken into hospital while they were still under the influence of an opiate. The second measurement followed in the morning of the 2nd day of the stay in hospital while they already had a withdrawal syndrome, which was rated by the physician of the intensive care unit by means of the revised WANG scale. After the second investigation the patients were given 10 mg methadone orally. One hour after medication the third measurement was carried out. The fourth examination was accomplished 1 day after the administration of the maximum dose of methadone. The fifth measurement followed on the day when half of the maximum dose was reached. The last investigation was carried out 48 h after the last minimum dose of methadone had been given (Fig. 1).

The aim of our investigation was to answer the question whether or not it is possible to evaluate the course of gradual opiate detoxification by means of static and light-evoked dynamic pupillometry.

Statistical Analysis. Statistical analysis included two-way variance analysis, discriminant analysis, the multiple Wilcoxon test and the Newman-Keuls test (Sachs 1977; Cooley and Lohns 1971).

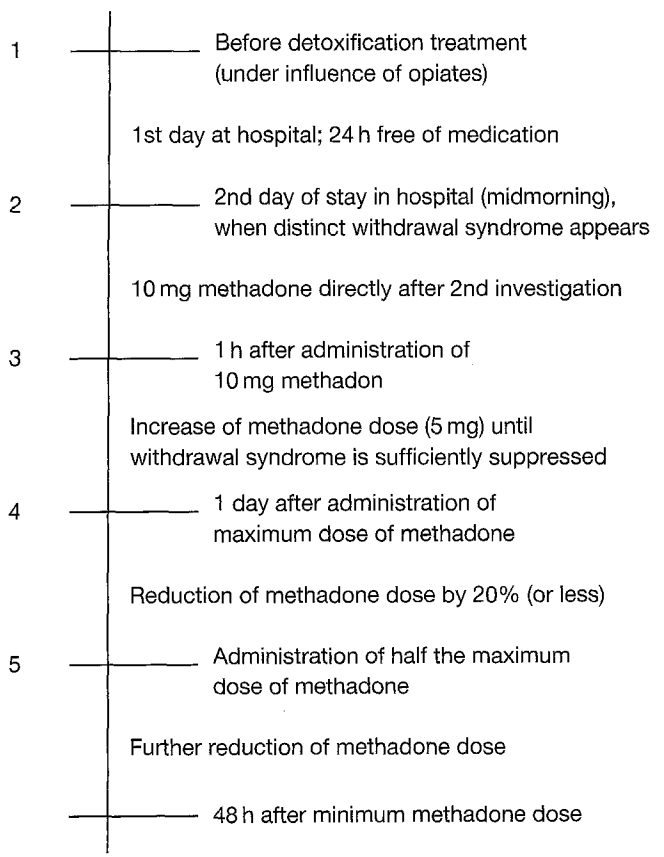

Fig. 1. Design of investigation

Results

Pupillary Diameter

Pupillary diameter showed a significant change over time ($F = 7.164$; $P<0.01$). The Newman-Keuls test demonstrated significant differences between the first measurement under the influence of the drug and the second measurement when the effects of the detoxification treatment already showed ($P<0.05$). That is to say, there was an evident dilatation of the pupil. After the fifth measurement (half of the maximum dose) and the sixth measurement (48 h after the last minimum methadone dose), there was a significant widening of the pupil in comparison with the first measurement ($P<0.05$ and $P<0.01$ respectively; Newman-Keuls test) (Fig. 2).

Spontaneous Fluctuations

Spontaneous fluctuations in drug-addicted patients during the course of therapy were increase in number. This increase reached the level of significance 1 h after the administration of 10 mg methadone (third examination) ($P<0.05$; Wilcoxon test). Between the third and the fourth measurements there was a massive reduction in fluctuations. Between the fourth and the sixth investigation fluctuations increased again. Comparing the first

Fig. 2. Course of detoxification treatment in opiate-addicted patients ($n = 29$). Static pupillometry, pupillary diameter. * $P < 0.05$; ** $P < 0.01$ (Newman Keuls test)

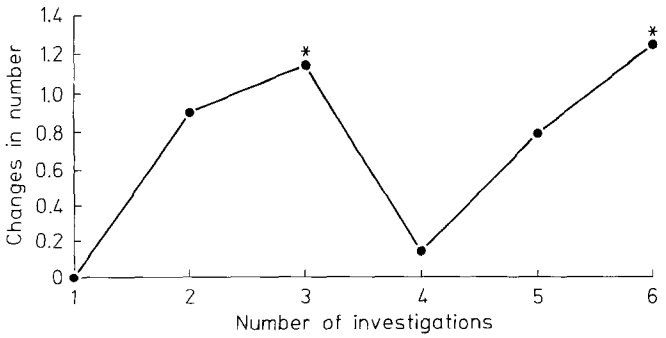

Fig. 3. Course of detoxification treatment in opiate-addicted patients ($n = 29$). Static pupillometry, spontaneous fluctuations. * $P < 0.05$; ** $P < 0.01$ (Newman Keuls test)

Fig. 4. Course of detoxification treatment in opiate-addicted patients ($n = 29$). Dynamic pupillometry, onset latency. * $P < 0.05$; ** $P < 0.01$ (Newman Keuls test)

and the last examination, the number of fluctuations rose significantly ($P<0.05$) (Fig. 3).

Onset Latency

Using dynamic pupillometry in addicted patients, a shortening of onset latency was observed after the withdrawal syndrome had appeared. Afterwards, the latency increased up to the sixth measurement, i.e. 48 h after the last minimum methadone dose (Fig. 4). These changes, however, did not reach the level of significance.

Relative Change

The relative change in pupillary diameter between the first measurement (while the subject were still under the influence of the drug) and the second investigation (by which time the distinct withdrawal syndrome had appeared) after exposure to an optical stimulus increased clearly; thereafter it decreased slightly. After the patients had received half the maximum dose, 48 h after they had taken the minimum dose of methadone (fifth and sixth investigations) there was a further increase in the relative change, reaching the level of signifcance in the Newman-Keuls test ($P<0.05$; $P<0.01$). The result was confirmed in the multiple Wilcoxon test. In the same test, the changes between the first and the second examination reached the level of significance ($P<0.05$; $P<0.05$; $P<0.01$) (Fig. 5). Multivariate analysis showed

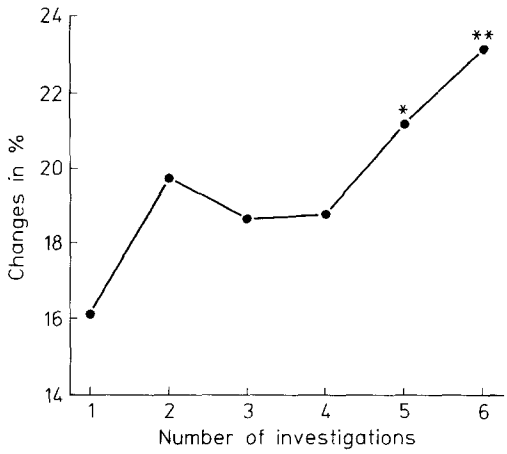

Fig. 5. Course of detoxification treatment in opiate-addicted patients ($n = 29$). Dynamic pupillometry, relative change. * $P < 0.05$; ** $P<0.01$ (Newman Keuls test)

significant changes during the course of therapy, which corresponds to the results described above.

Self-rating

Subjective well-being and withdrawal distress were evaluated by the FEO scale. Between the first (under influence of opiate and the second measurement (withdrawal syndrome) no significant differences could be observed. However, the total score of the FEO scale differed significantly between the second measurement and the fourth, fifth and sixth ($P<0.05$; 0.01; 0.05; Duncan test). Only a small difference between the second and the third measurement, which did not reach the level of statistical significance, was observed. While the subjective well-being and the vegetative complaints of the patients showed a deterioration when a distinct syndrome appeared, a slight improvement was observed after the administration of 10 mg methadone. The total score of the FEO scale revealed a marked improvement in the course of treatment.

Discussion

Using static and dynamic pupillometry, we whished to investigate whether or not measurement of the pupil is a sensitive indicator for the course of detoxification treatment. Firstly, the vertical pupillary diameter was measured. The pupil that had been constricted under the influence of the opiate showed a significant widening (approximately 0.6 mm) on the 2nd day of the stay in the hospital when the withdrawal syndrome had appeared. Directly after the beginning of the gradual detoxification treatment with methadone, the pupillary diameter decreased as expected and remained so after the maximum dose had been given. At that time the pupil was still wider than it was when the subject was under the influence of the previous drug. After administering half the maximum dose (fifth investigation) the pupil dilated again and towards the end of therapy reached a diameter

comparable with that in healthy normals (sixth examination). This successive widening of the pupil might correspond with the protracted withdrawal. Summing up, all clinical findings could be measured psychophysiologically, i.e. by means of static pupillometry and by means of the FEO scale. Stimulating the locus ceruleus in monkeys, electrically or pharmacologically, changes were produced that strongly resembled those appearing during opiate withdrawal (Gold et al. 1977). While opiates lock the activation of the most important noradrenergic nucleus of the brain through opiate receptors (Aghajanian et al. 1978), there might be an increase in noradrenergic activity in certain areas, such as the locus ceruleus, while withdrawing from opiates. As the dilator muscle of the pupil is innervated by nerve fibres that use noradrenaline as the transmitter, the widening of the pupil is comprehensible. For dilatation of the pupil, the somato-psychic condition of the patient also plays an important role. Moreover, the reaction of the pupil reflects the central condition, which is difficult to assess but has to be taken into consideration when interpreting the results. The spontaneous fluctuations (amplitude: >0.3 mm)of the pupils have been discussed as an indicator of central activation (Lowenstein et al. 1963; Grünberger et al. 1988a) The number of fluctuations increased in comparison with the initial value (before withdrawal) and reached a maximum 1 h after oral administration of 10 mg methadone. Therefore, the subjects showed a central activation which could not be suppressed by 10 mg methadone. Only the maximum quantity stopped activation. After the application of half the maximum dose (fifth measurement) and 48 h after the subject received the last minimum methadone dose, a massive increase in central activation was observed. The latency time which was shortened because of the opiate which the subject had consumed, decreased even further as the withdrawal syndrome occurred. That is to say that stimuli were processed very fast. This might be the result of the fact that patients are more vigilant and excitable when the withdrawal syndrome appears. After methadone treatment had been started the latency increased; after administration of the maximum dose it decreased slightly and it approximated the values found in healthy normals towards the end of the treatment. From the results of dynamic pupillometry, it is clear that psychotropic substances, directly and/or indirectly via changes in the subject's emotional condition, modified the reaction of the pupil to light. An important variable of dynamic pupil measurement is the relative change (i.e. change of the pupil in percent as compared with the initial value). An increase in the relative change was clearly seen when the withdrawal syndrome occurred; moreover when half of the maximum dose was given and 48 h after administration of the minimum quantity of methadone. Ten milligrams, or the maximum dose of methadone, decreased the relative change. The reactivity of the pupil, as reflected by the dynamic factor in our factor analylsis (Grünberger et al. 1987), improved in the course of the treatment and approached the values found in healthy normals. Our pupillary measurements corresponded not only with clinical observations but also with the self-evaluation by means of the FEO questionnaire. The total scores of the self-ratings improved in the course of detoxification; at the end of treatment better scores than before the start of treatment were obtained. Thus it seems possible that no methadone withdrawal syndrome appeared in the patients. On the whole, the measurement of pupillary changes seems to be a useful instrument for assessing the course of withdrawal treatment, thereby preventing the patient from being subjected to an unnecessarily long treatment period or high doses of substitute drugs.

References

Aghajanian GK (1978) Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal response to clonidin. Nature 276:186–187

Cooley WW, Lohnes RP (1971) Multivariate data analysis. Wiley, New York

Gold MS, Redmond DE Jr (1977) Pharmalogical activation and inhibition of noradrenergic activity alter specific behaviours in nonhuman primates (abstract). Neurosci Abstr 3:250

Grünberger J, Linzmayer L, Saletu B (1984a) Psychodiagnostik mit Hilfe psychophysiologischer Verfahren. Wien Med Wochenschr 2:29

Grünberger J, Linzmayer L, Saletu B, Stöhr H (1984b) Mikrocomputer im Einsatz bei Routineuntersuchungen und Forschungsaufgaben im Bereich der klinischen Psychodiagnostik. Biomed Tech 29:283

Grünberger J, Linzmayer L, Saletu B, Stöhr H (1984c) Zur Methodologie der Pupillenmessung. Psychiatr Clin 3:157

Grünberger J, Linzmayer L, Gathmann P, Saletu B (1985) Computerassistierte „statische" und lichtevozierte „dynamische" Pupillometrie bei psychosomatischen Patienten. Wien Klin Wochenschr 20–775

Grünberger J, Linzmayer L, Cepko H, Saletu B (1986a) Pupillometrie im psychopharmakologischen Experiment. Arzneim Forsch 1:141

Grünberger J, Linzmayer L, Küfferle B, Saletu B (1986b) Pupillometrie bei schizophrenen Patienten. In: Keup W (ed) Biologische Psychiatrie. Springer, Berlin Heidelberg New York, p 199

Grünberger J, Linzmayer L, Cepko H, Saletu B (1987a) Lichtevozierte dynamische Pupillometrie zur Differenzierung psychotroper Substanzen. Arzneim Forsch 3:357

Grünberger J, Linzmayer L, Witek R, Saletu B (1987b) Faktorenanalytische Untersuchungen und Reliabilitätsbestimmung der statischen und dynamischen Pupillometrie. Wien Med Wochenschr 7:135–139

Grünberger J, Linzmayer L, Gasic S, Saletu B (1988) Computerassistierte statische und dynamische Pupillometrie zur Charakterisierung des trizyklischen Antidepressivums Cianopramin. Arzneim Forsch 3:383–387

Grünberger J, Linzmayer L, Suletu B, Lesch OM (1989) Klinische psychologische Diagnostik bei ambulanten Alkoholikern: Statische und lichtevozierte dynamische Pupillometrie. Wien Z Suchtforsch 12:53–62

Kolb L, Himmelsbach CK (1938) Clinical studies of drug addiction. III. A critical review of the withdrawal treatments method of evaluating abstinence syndromes. Am J Psychiatry 94:759–799

Loimer N, Linzmayer L, Grünberger J, Presslich O (1988) Objektivierung des Entzugssyndroms während der Ultrakurzentzugsbehandlung mit hohen Naloxondosen bei Opiatabhängigkeit. Therapiewoche Österreich 12. pp 1125–1130

Sachs L (1977) Statistische Auswertungsmethoden. Springer, Berlin Heidelberg New York