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EXTENDED REPORT

Orthoptic status before and immediately after heroin detoxification

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Aim: To determine whether changes in orthoptic status take place during withdrawal from heroin and/or methadone.

Method: A prospective study of patients, using a repeated measures design, attending a 5 day naltrexone compressed opiate detoxification programme.

Results: 83 patients were seen before detoxification (mean age 27.1 (SD 4.6) years) and 69 after detoxification. The horizontal angle of deviation became less exo/more eso at distance ($p<0.001$) but no significant change was found at near ($p=0.069$). Stereoacuity, visual acuity, and convergence were found to be reduced in the immediate post-detoxification period. Prism fusion range, refractive error, subjective accommodation, and objective accommodation at 33 cm did not reduce but a small decrease was found in objective accommodation at 20 cm.

Conclusions: The eso trend found in these patients may be responsible for the development of acute concomitant esotropia in some patients undergoing heroin detoxification. However, the mechanism for this trend does not appear to be caused by divergence insufficiency or sixth nerve palsy.

Himmelsbach[1] stated: "Occasionally a patient will complain of double vision" on abrupt withdrawal from heroin. The incidence of "diplopia and/or blurred vision" during withdrawal has been reported as between 10% and 33.3%.[2] Conversely, in a series of 100 patients admitted to a drug treatment centre, none complained of a change in vision.[3] Small case series of patients presenting with esotropia following heroin detoxification have appeared in the literature[4–6] and diplopia has been associated with the use of chlorpromazine (Largactil) in one patient.[7] Exotropia has been reported in two cases on intake of heroin.[6]

This study was undertaken to determine the incidence of problems immediately after heroin and/or methadone detoxification and to record orthoptic and refractive measurements before and immediately after detoxification. Further, patients are compared with a control group.

METHODS

Patients were recruited over 9 consecutive weeks, from an in-patient heroin detoxification centre at which a 5 day naltrexone compressed opiate detoxification protocol is used (table 1).[8] Each patient was seen twice—once before detoxification (day 1) and once before discharge (day 5). Information sheets and consent forms were sent to patients before admission. Consent was obtained on the day of admission. Exclusion criteria were: presbyopes or pre-presbyopes (41 years of age and above); severe learning difficulties; neurological disorders; visual acuity of less than 6/60 in both eyes; visual acuity of less than 3/60 in either eye. Staff from the centre volunteered as control participants and followed the same exclusion criteria and procedure as below. The study was approved by the local research ethics committee.

On the day of admission (day 1), before sedation, consenting patients underwent examination by one researcher (AYF). All tests were performed with refractive correction, if worn regularly. The order of testing was as in the order of the description below. Details of other drug use before admission and mode of opioid use were taken from hospital notes.

For patients admitted in weeks 3–9, the time since the last use and the time until the next heroin or methadone dose would usually be taken were noted.

A cover test was performed at 33 cm and 6 metres. If a subject was found to have a decompensating deviation at near, the binocular visual acuity (BVA) was recorded. Horizontal prism fusion range to a light target with Bagolini glasses, was measured noting the break point (point at which fusion failed). For analysis, the angle of deviation (minus value for exo deviations and plus for eso deviations) was added to the value of the prism at break point (absolute value). In manifest strabismus the prism fusion range was not undertaken. Stereoacuity was assessed using the TNO stereotest. Prism cover test measurements were recorded; and on right gaze and left gaze at 6 metres for subjects tested in weeks 4–9. Monocular near visual acuity was measured using a reduced Snellen chart and distance visual acuity at 100% and 10% contrast using a Bailey-Lovie chart. Ocular movements were assessed fixing a light and using a cover test. Pupil size was assessed with a millimetre rule fixing the examiner's eye at approximately 50 cm. Using the RAF rule, convergence was recorded and subjective accommodation for both eyes open; each eye monocularly; and both eyes open repeated. Objectively, refractive state was measured in either eye (with both eyes open) using the Nikon open field autorefractor SRW 5000 while the subject was fixing at 6 metres (with and without fogging lens); 33 cm, and 20 cm to a 6/6 target or smallest letter able to be seen.

On the morning of day 5 the same protocol was used for performing the clinical tests, but some subjects were unwilling or unable to complete testing because of tiredness or sickness. Patients were asked if they had noticed any problems with vision. The same examiner (AYF) repeated the tests but did not refer to previous data sheets until testing was completed. All tests were carried out in the same area on both days under normal room lighting conditions, with the

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Table 1 Five day detoxification programme

Time	Medication	Purpose
Afternoon day 1 through to midnight day 3	Zuclopenthixol (Clopixol) 10 mg and diazepam (Valium) 10 mg orally, then zuclopenthixol 4×10 mg daily with another four doses as and if required and diazepam 4×10 mg daily. Trazodone hydrochloride 150–300 mg nightly.	Sedation
	Lorazepam (Ativan) up to 4 mg every 6 hours; chlorpromazine 50–100 mg every 6 hours for those with high tolerance to the standard medication, or where patients have been abusing benzodiazapines. Amylobarbitone/quinalbarbitone (Tiunal) 100 mg−200 mg every 6 hours if further top up needed	Additional medication if sedation not adequate
Day 4	Challenge dose of oral 25 mg naltrexone (Nalorex)	To flush out remaining opiates
Day 5	Full naltrexone (Nalorex) dose (50 mg)	To build block against opiate use
Throughout	Diclofenac sodium (Voltarol); hyoscine butylbromide (Buscopan); ranitidine (Zantac); procyclidine (Kemadrin); prochlororperazine (Stemetil), metoclopramide (Maxolon) as required.	To relieve symptoms or side effects of other medication

exception of three cases on day 5 who were unwell; limited testing took place in these patients' rooms.

Analysis

Near visual acuity[9] and prism measurements are ordinal data and non-parametric tests used (Wilcoxon signed ranks test (WSRT); Mann-Whitney (MW); Friedman test). Parametric analysis involved the use of t test (paired or unpaired) and analysis of variance. Spearman's test was used to determine correlations and multivariate regression. Refractive data were converted to mean spherical equivalent (MSE) for analysis.

RESULTS

Eighty three subjects were seen before detoxification, mean age 27.1 (SD 4.6) years (range 18–40.5). Fifty five were currently heroin users; 18 used methadone but topped up with heroin; and 10 were currently using methadone only. The mode of heroin use was or had been smoking 35; intravenously 25; both 20. The remaining three subjects used methadone and had rarely used heroin. Sixty nine subjects were examined on day 5. Ten subjects formed the control group, mean age 29.5 (7.4) years (range 20–39).

Seven patients were myopic and two hypermetropic. One patient had had a blow to his left eye which resulted in intermittent diplopia. One patient reported diplopia following a previous detoxification attempt and one patient reported diplopia if he started to withdraw from heroin.

Table 2 Number of patients using heroin substitutes and non-prescribed drugs

	Regular	Irregular/occasional/in past
Methadone	28	55
DF118	5	36
Cocaine	47	3
Cannabis	46	1
LSD	26	1
Ectasy	38	0
Amphetamines	15	1
Temazepam	24	16
Diazepam	26	20
Nitrazepam	8	6
Codeine	0	3
Zopiclone	0	5
Amitryptiline	0	1

The mean time from the last dose of heroin was 8.44 (7.76) hours (n = 53) and all except nine would normally have used it again by the time of examination. The use of non-prescribed drugs was frequent and listed in table 2 along with prescribed heroin substitutes.

Fifty of 69 subjects seen on day 5 reported ocular symptoms. While the majority (n = 22) noted these on day 4, others noted them occurring across the other days (mainly days 1–3). On day 5, 26 felt that symptoms were improving, one worsening, and there was no change in the others. Symptoms were blur all distances n = 12; blur near only n = 1; blur distance only n = 4; diplopia n = 14; blur and diplopia n = 19.

Cover test and angle of deviation

Cover test findings are shown in table 3 and angles of deviations in table 4. The angle was significantly different between patients on day 1 and controls (p = 0.005, MW) for near but not for distance (p = 0.055 MW). Median values and ranges for horizontal prism cover test measurements for the patient group for near and distance are shown in table 4. The change in horizontal angle of deviation for paired subjects between day 1 and day 5 was not significant (p = 0.069) for near but was significant for distance (p<0.001), demonstrating a change in the eso direction. There was no difference between those withdrawing from heroin, methadone, or a combination of the two, and no effects from other recreational drugs taken.

Primary position distance and lateral gaze measurements for 38 subjects where data were complete for days 1 and 5 are given in table 4. For day 1 and for day 5 a significant difference was shown between primary position, right and left gaze (both p<0.01; Friedman). To determine whether there was a change in the degree of incomitance, the change in the angle between primary position and side gaze between day 1 and day 5 was considered and resultant measurements compared. Right gaze measurements showed a median change of +2Δ (range −12Δ to +10Δ), not significant (p = 0.098), and left gaze measurements showed a median change of +2Δ (range −8Δ to +10Δ), significant (p = 0.01). Only one subject in the patient group demonstrated a vertical deviation in the primary position, this was the patient who gave the history of injury; no vertical deviation was detected on day 1 (N: 20Δ X for near; 2Δ X for distance) but on day 5 a vertical element was present at both distances (N: 20ΔXT 4ΔRHT near; φ 6Δ RHT distance).

Table 3 Cover test findings (numbers refer to number of patients)

	Controls	Day 1	Day 5	Controls	Day 1	Day 5
	Near	Near	Near	Distance	Distance	Distance
E	2	9	19	1	9	18
E(T)	0	0	0	0	0	5
ET	0	0	1	0	0	16
X	7	59	37	5	55	14
X(T)	0	12	7	0	2	0
XT	0	0	2	0	1	0
O	1	3	3	4	16	13
Total	10	83	69	10	83	66

E = esophoria; E(T) = intermittent esotropia; ET = esotropia; X = exophoria; X(T) = intermittent exotropia; XT = exotropia; O = orthophoria.

Prism fusion range

Median values for the total fusion range for control subjects were 41.5Δ for near (range 24–53) and 23Δ for distance (range 8–33). For the patient group total amplitudes were 26Δ near (range 2–70; n = 69) and 18Δ distance (range 4–34; n = 68) on day 1 and 24Δ near (range 2–57; n = 45) and 14.5Δ (range 3–39; n = 32) on day 5. The range was significantly higher for control subjects compared with patients on day 1 at near but not distance (p = 0.013 and p = 0.494 respectively, MW). The difference at near was due to the divergent range being lower in the patient group when the baseline angle of deviation was taken into account.

No statistical difference existed in the total prism fusion range between day 1 and day 5 for near or distance either when all patients were considered (p = 0.452; p = 0.063 respectively, MW), or when pairing data where complete for both examinations (p = 0.189; p = 0.45 respectively, WSRT), and no significant change in absolute divergence occurred at distance fixation (median day 1−6Δ; median day 5−7Δ; p = 0.806. WSRT). The control subjects showed a similar absolute range of divergence at distance (median 6Δ) to the patient group (p = 0.791, MW).

Stereoacuity

No difference was found between control subjects and patients on day 1 (median 60 seconds of arc, p = 0.752, MW). Twenty nine of 60 patients for whom measures were available on both days showed a reduced score (p<0.0001. WSRT). Of the 12 patients showing an intermittent exotropia at near on day 1, 10 achieved 60 seconds of arc or better. All had normal binocular visual acuities.

Ocular motility

Ocular motility was within normal limits on day 1 in 54 subjects. Twenty four showed very small limitations of abduction (<−1) and five had other defects (four cases: slight unilateral or bilateral superior oblique underactions, one case: slight underaction left superior rectus (−1)

following injury). Of those tested on day 5 (n = 60), 35 were normal, 19 showed very small limitation(s) of abduction, four subjects had developed signs of superior oblique underaction(s), and one inferior oblique underaction. The one case with underaction in laevoelevation showed an increase in this (−2).

Visual acuity, convergence, and accommodation

Near visual acuity had a median of 0.00 (6/6) for both right and left eyes for control subjects and patients on day 1 and 0.2 for patients on day 5. A significant decline was shown between day 1 and day 5 (p<0.001 right eye; p = 0.006 left eye. WSRT). Distance visual acuity and low contrast acuity also significantly declined in the absence of any change in refractive error (table 5). Convergence, accommodation and pupil size results are shown in table 5.

Medication

The only statistically significant finding was a negative correlation between the dosage of Clopixol and the change in the eso direction (r = −0.272; p = 0.033). The r^2 value is low.

DISCUSSION

The main finding of the study was the change in the distance angle of deviation, demonstrating a change in the eso direction. The most obvious mechanisms for this are sixth nerve involvement and divergence insufficiency. When this trend became apparent, lateral gaze measurements were added to the testing regime (week 4 onwards). The median change in side gaze measure, however, was only 2Δ and this is not considered clinically indicative of sixth nerve weakness. Also there was a tendency for a change in the eso direction on side measures before detoxification.

Subtle sixth nerve involvement has been implicated in divergence paralysis[10] because of raised intracranial pressure and in the presence of papilloedema and the condition has been reported with ingestion[11] and withdrawal of diazepam.[12]

Table 4 Horizontal prism cover test measurements

	Day 1			Day 1			Day 5		
	Controls	Median	Range	Patients	Median	Range	Patients	Median	Range
Near	n = 10	3Δ PBIn	8Δ PBIn to 8Δ PBOut	n = 82	8Δ PBIn	25Δ PBIn to 35Δ PBOut	n = 67	6Δ PBIn	30Δ PBIn to 18Δ PBOut
Distance	n = 10	1.5Δ PBIn	2Δ PBIn to 4Δ PBOut	n = 83	2Δ PBIn	12Δ PBIn to 4Δ PBOut	n = 66	4Δ PBOut	14Δ PBIn to 16Δ PBOut
Primary position				n = 38	2Δ PBIn	10Δ PBIn to 4Δ PBOut	n = 38	4Δ PBOut	14Δ PBIn to 16Δ PBOut
Right gaze				n = 38	1.5Δ PBIn	4Δ PBIn to 8Δ PBOut	n = 38	8Δ PBOut	12Δ PBIn to 18Δ PBOut
Left gaze				n = 38	2Δ PBIn	6Δ PBIn to 8Δ PBOut	n = 38	7Δ PBOut	14Δ PBIn to 18Δ PBOut

PBIn = prism base-in; PBOut = prism base-out; Δ = prism dioptres.

Table 5 Test results (mean (SD))

Test and notation	Controls	All patients completed day 1	p Values Control v day 1	Day 1 (paired data)	Day 5 (paired data)	p Value and number of pairs
Distance RVA (logMAR)	−0.01 (0.08)	0.00 (0.24)	0.563	0.01 (0.27)	0.11 (0.15)	0.001* 55
Distance LVA (logMAR)	0.02 (0.09)	0.09 (0.03)	0.833	0.02 (0.25)	0.13 (0.22)	<0.001* 55
Low contrast RVA (logMAR)	0.22 (0.1)	0.25 (0.16)	0.492	0.24 (0.16)	0.32 (0.16)	<0.001* 49
Low contrast LVA (logMAR)	0.25 (0.11)	0.25 (0.16)	0.941	0.24 (0.14)	0.3 (0.15)	0.003* 48
Pupil size RE (mm)	4.65 (0.66)	4.52 (1.22)	0.745	4.65 (1.24)	4.96 (1.14)	0.109 62
Pupil size LE (mm)	4.65 (0.67)	4.53 (1.23)	0.781	4.67 (1.25)	4.93 (1.21)	0.194 62
Convergence (cm)	7 (1.56)	7.72 (3.56)	0.531	7.49 (3.83)	10.96 (10.11)	0.012* 53
Accommodation RE (cm)	15.3 (5.58)	15.29 (5.52)	0.995	14.63 (5.14)	15.69 (5.31)	0.267 48
Accommodation LE (cm)	15.9 (7.4)	15.08 (5.18)	0.658	14.61 (4.72)	15.69 (4.98)	0.179 49
Accommodation BE (cm)	13.1 (3.2)	12.93 (4.58)	0.908	13.22 (4.85)	14.15 (6.68)	0.278 53
Accommodation BE repeated (cm)	14.5 (6.85)	12.2 (4.16)	0.139	12.24 (4.2)	13 (5.1)	0.356 42
MSE with fogging lens RE (D)	+0.05 (0.23)	+0.16 (0.85)	0.688	+0.06 (0.63)	+0.26 (0.69)	0.129 28
MSE with fogging lens LE (D)	+0.46 (0.34)	+0.14 (0.63)	0.14	+0.08 (0.44)	+0.22 (0.53)	0.093 26
MSE 6 metres RE (D)	+0.08 (0.45)	+0.1 (0.75)	0.929	−0.02 (0.51)	0.068 (0.68)	0.308 36
MSE 6 metres LE (D)	+0.25 (0.54)	0.11 (0.56)	0.477	+0.18 (0.49)	0.19 (0.67)	0.851 35
MSE 33 cm RE (D)	−2.34 (0.18)	−2.34 (0.58)	1.00	−2.44 (0.36)	−2.35 (0.55)	0.373 30
MSE 33 cm LE (D)	−2.4 (0.29)	−2.38 (0.44)	0.896	−2.37 (0.43)	−2.26 (0.85)	0.443 29
MSE 20 cm RE (D)	−3.74 (0.42)	−3.9 (0.67)	0.456	−4.05 (0.63)	−3.49 (0.81)	0.003* 26
MSE 20 cm LE (D)	−3.86 (0.59)	−3.88 (0.67)	0.924	−3.87 (0.56)	−3.28 (0.77)	<0.001* 26

RVA = right visual acuity; LVA = left visual acuity; RE = right eye; LE = left eye; BE = both eyes; MSE = mean spherical equivalent; D = dioptres; *significant results.

Jacobson[13] reports two series of primary and secondary cases of divergence insufficiency, median absolute divergence amplitudes were 2Δ and 4Δ respectively. Median values in this current study for 6 metres were 6Δ on day 1 and 7Δ on day 5, and no significant change was found. However, although subjects who developed esophoria and intermittent esotropia were included in the day 5 measurements, subjects where a constant manifest deviation developed did not have their angle corrected and the test performed. The level of divergence was comparable to the control group on both day 1 and day 5 of the study at distance. The lower level of divergence at near could be an artefact in that 15 of the patient group and no controls diverged to as much as their angle of deviation and so had a ''negative'' level of divergence. This phenomenon is often seen clinically in exophoric patients and is possibly a carryover of tenacious proximal convergence.

Following a single dose of lorazepam 0.038 mg/kg Speeg-Schatz et al[14] found a change of +2.8Δ at distance fixation and reduction of the near point of convergence by a mean of 6.3 cm without any change in subjective accommodation. The effect was thought to be due to muscle relaxation. Two drugs in the phenothiazine group have also been linked to diplopia: olanzapine[15] causing a concomitant esotropia and prochlorperazine[16] causing sixth nerve palsy. However, no links were found between lorazepam or phenothiazine doses and changes in distance angle in this study.

No differences were found in subjective accommodation between controls and patients, before and after detoxification, and no fatigue between the first and last measure. This is contrary to Perez et al's findings[17]; they reported reduced subjective accommodation in a group of heroin users in a detoxification centre. However, the method of detoxification is not given, nor stage during detoxification at which measurements were taken. ''Visual disturbances'' or ''blurred vision'' are listed as side effects for several of the medications used in this withdrawal programme; however, there was no evidence of reduced accommodation on subjective testing and only weak evidence for reduced objective accommodation (table 5).

The number of subjects reporting blur and/or diplopia was 72.5%, higher than the 10% to 33.3% previously reported.[2] This may be due to the method of detoxification. Kowal et al[5] reported that diplopia was more common following rapid detoxification (using naltrexone) and this has also been suggested[4] as causing a ''physical or psychic shock'' which precedes the onset of acute concomitant esotropia.[18] In the current study, cover test findings showed intermittent esotropia to be present in 10 of 14 subjects complaining of diplopia. In 17 patients diplopia was accompanied by blur, and only seven of these demonstrated a manifest deviation. This is suggestive that some patients are interpreting blur as diplopia. Pupil size was similar before and after detoxification and so could not account for blur.

Visual acuity reduction was not due to refractive changes. In a previous study ophthalmoscopic examination was found to be normal following withdrawal.[3] Opioid receptors have been identified in the ganglion cell layer of the human

retina[19] and withdrawal from opiates may affect the firing rate or neurotransmission of these cells.

Opioid receptors in many parts of the brain have yet to be identified. The onset of exotropia on intake[6] of heroin and esotropia on withdrawal[4–6] and the larger exo deviations at near in the patient group is suggestive of an active mechanism. Although the number of participants in the control group was small, the angle of deviation in the group compares well with previously published literature.[20] The main difference found was that, despite the presence of eso deviations in nine of 83 patients and only two of 10 controls (no statistical difference shown by χ^2 testing for these figures), the angle of deviation in the patient group was significantly greater and this difference was in the exo direction. This was statistically significant for near only, although a trend towards this could also be said to exist in the distance, results just failing to reach the 5% level of significance ($p = 0.055$). The range of angles was also much higher in the patient group. It has been hypothesised that there is direct involvement of mid brain neurons in the onset of acute concomitant esotropia,[21] and it is possible that cells involved in the near or far response[22–25] are affected such that the equilibrium between convergence and divergence is altered as tolerance to opioids increases leading to an imbalance on withdrawal.

This study has demonstrated an eso trend at distance fixation following detoxification. The mechanism does not appear to be divergence insufficiency or sixth nerve involvement, nor does it appear to be related to medication used during this detoxification programme. The mechanism remains speculative. However, where adult patients present with distance esotropia, or a history of intermittent diplopia which has now become constant and esotropia is present, the history should include questions pertaining to drug abuse.

ACKNOWLEDGEMENTS

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