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CARDIOVASCULAR, RESPIRATORY AND TEMPERATURE RESPONSES TO INTRAVENOUS HEROIN (DIAMORPHINE) IN DEPENDENT AND NON-DEPENDENT HUMANS

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1 Intravenous heroin (diamorphine) was administered to volunteers, in doses of 2.5 and 5 mg to non-dependent and doses of 1/6, 1/3 and ½ of their prescribed daily dose of opiates to dependent subjects, and heart and respiration rates, blood pressure, body and skin temperature and skin conductance were measured before and for 2 h after injection.

2 Heart rate fell and continued to fall after injection in both groups of subjects although the time course was different in the two groups. This was thought to be a non-specific effect of heroin.

3 Respiration rate fell after injection in both groups. The dependent group showed a faster recovery of pre-drug respiration rate. This was interpreted as being due to tolerance in the dependent group.

4 Systolic blood pressure fell only in the dependent group and diastolic blood pressure only fell after injection of the largest dose of heroin in both groups.

5 Body temperature fell after injection of heroin in a similar way in both groups while neither skin temperature nor skin conductance changed. This was interpreted as a drug-induced alteration in thermo-regulatory mechanisms.

6 Placebo had no effect on any of these measures. There were no differences between the responses of the high and low dose dependent subjects to different doses of heroin nor did prior ingestion of methadone affect any of the measures.

Introduction

Previous authors have reported results from a project carried out on the effects of intravenous heroin (diamorphine) in opiate dependent and non-dependent volunteers. These concerned plasma morphine concentrations and pupil diameters and tolerance (Tress, Aherne, El-Sobky, Piall & Marks, 1977; Tress, El-Sobky, Aherne & Piall, 1978; Tress & El-Sobky, 1979). The present study reports further results from the same projects using measurements of heart rate, respiration rate, blood pressure, body temperature, skin temperature and skin conductance.

The aim of the study was to compare the responses of the opiate dependent and non-dependent humans to intravenous heroin with particular reference to the development of tolerance to the effects of heroin. The results of the pupil diameter measurements have been reported by Tress & El-Sobky (1979). Pupil measurements showed tolerance in not only the size of the response to heroin but also in the time course of the response. In addition the previous ingestion of methadone (as part of the dependent subject's opiate prescription from the drug clinic he attended) altered the pupillary response to heroin. The effects of intravenous heroin on heart rate, respiration rate, blood pressure, skin and body temperature and skin conductance are examined in this paper. The results are compared with the results from the pupil measurements with particular reference to the size and time course of the response to heroin and to the effect of prior ingestion of methadone.

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Methods

The method of obtaining subjects, ethical considerations and criteria for accepting subjects have all been described in detail elsewhere (Tress & El-Sobky, 1979). Briefly the non-dependent subjects were five male volunteers from the staff of the Unit and Medical School who were screened as suitable by a psychiatrist prior to testing. The volunteer dependent subjects (18: 12 male, 6 female) were patients being treated for heroin dependency. All dependent subjects were receiving maintenance doses of heroin (12 subjects) or heroin plus oral methadone (the methadone not exceeding half the total quantity of prescribed drug) (6 subjects). The dependent subjects were also subdivided into a high dose group (prescribed 70 mg or more opiates per day) and a low dose group (prescribed 65 mg or less opiates per day). There were six heroin users and three heroin plus methadone users in both groups.

The non-dependent subjects were tested on three occasions, separated by at least 1 week and on each test day were given an intravenous injection of 2.5 mg heroin or 5 mg heroin or saline placebo in random order. The dependent subjects were admitted to the Unit for 5 days and were tested on the final 3 days with intravenous heroin injections of ½, 1/3 and 1/6 of the total daily prescription of opiates (heroin or heroin plus methadone). A saline placebo injection was given to the dependent subjects 40 min before the heroin injection on the second test session as dependent subjects were unable to tolerate an inactive injection for longer than this. When methadone was part of the prescription it was taken at least 12 h before the tests were made. Apart from these differences in treatment between dependent and non-dependent subjects the procedures were the same for both groups.

Testing was carried out in a sound-attenuated, air conditioned chamber, kept at 21°C ± 1°C, in which the subject reclined in a chair. Heart rate, respiration rate and body temperatures were recorded continuously for 10 min periods while the subject rested in the chair. Blood pressure was measured at the end of the 10 min period along with pupil diameter and a sample of blood was taken. Two repetitions of this procedure were carried out before the heroin injection and five repetitions were made after the injection. Heart rate was measured using a photoplethysmograph on the index finger of the non-preferred hand, respiration rate was measured with a mercury strain gauge across the chest, body temperature was monitored by means of an aural thermistor (used alone) and blood pressure was measured blind using a London School of Hygiene and Tropical Medicine sphygmomanometer. Skin temperature was measured by a thermistor 6 mm in diameter taped to the small finger and skin conductance level by means of two silver/silver chloride cup electrodes filled with electrode paste and taped to the middle two fingers. The outputs from the tranducers were taken to preamplifiers and, in the case of the pulse and the respiration waves, through ratemeters. Heart and respiration rate and skin and body temperature and skin conductance levels were recorded on a chart recorder for later analysis. The procedures for analysing plasma samples for morphine levels and for measuring pupil diameter were as described by Tress *et al.* (1978). The setting-up procedure i.e. inserting cannula for the drip, affixing electrodes and tranducers and instructing the subject, took about 30 min during which time the subject's temperature was equilibrating to room temperature. The pre-injection testing lasted for a further 40 min.

Results

One non-dependent subject withdrew himself from the study after completing one test session with a dose of 2.5 mg heroin. He was concerned at his euphoric response to heroin and he preferred not to take heroin again. The results from the non-dependent subjects were therefore based on four complete sets

Table 1 *t*-values derived from Dunnett's test (heroin doses) and *t* tests (placebo doses) for heart rate, respiration rate, blood pressure and body temperature following drug injection in dependent subjects.

Dose of heroin	*Time from injection/t values*		
	10 min	*1 h*	*2 h*
Heart rate			
Placebo	0.30	—	—
1/6 daily dose	3.73**	7.02**	8.38**
1/3 daily dose	3.05**	5.15**	7.00**
½ daily dose	2.24**	5.14**	6.19**
Respiration rate			
Placebo	0.22	—	—
1/6 daily dose	3.00**	2.42*	1.60
1/3 daily dose	3.04**	3.12**	4.27**
½ daily dose	4.11**	2.76*	3.31**
Systolic BP			
Placebo	1.53	—	—
1/6 daily dose	3.52*	5.50**	4.91**
1/3 daily dose	0.09	2.69*	2.97**
½ daily dose	2.07	5.04**	5.04**
Diastolic BP			
Placebo	1.58	—	—
1/6 daily dose	1.67	2.84**	1.84
1/3 daily dose	0.68	0.70	0.22
½ daily dose	2.21*	2.49*	2.42*
Body temperature			
Placebo	1.05	—	—
1/6 daily dose	1.24	2.14*	2.27*
1/3 daily dose	0.83	4.18**	6.13**
½ daily dose	0.85	4.89**	7.02**

*$P<0.05$; **$P<0.01$.

of data. One dependent subject was able only to complete two test sessions due to illness. Three complete test sessions were achieved for the remaining 17 subjects on the blood pressure, skin temperature and skin conductance measurements but the heart rate, respiration rate and body temperature results were based on complete sets of data from 16 subjects each due to equipment failure.

The analysis carried out on the heart rate, respiration rate, blood pressure and body temperature data were as follows: Analyses of variance were carried out for each dose of drug and, for the non-dependent subjects placebo. After this Dunnett's test (Edwards, 1972) was carried out comparing measures at 10 min, 1 h, and 2 h after injection with pre-injection rates. The pre-placebo levels were compared with the 10 min post-placebo measures for the dependent subject groups using *t*-tests. The data are displayed as graphs in Figures 1, 2, 3 and 4 and the *t* values from the Dunnett's test and the *t* tests are shown in Tables 1 and 2. All post-drug measurements were corrected for pre-drug measurements by subtracting post-drug from pre-drug measurements and a further analysis of variance carried out across drug doses for each measurement and for each subject group. The results of these analyses are shown in Tables 3 and 4.

Heart rate

It can be seen that the effect of heroin on heart rate in the dependent subjects was a fall in heart rate after injection which continued throughout the test period. The fall in heart rate was not affected by the dose of heroin used.

The effect of heroin on heart rate in the non-dependent subjects was similar to the effect in dependent subjects—a fall in heart rate which continued throughout the test period. However, the onset of the effect was slower with no significant fall at 10 min after injection. Also the effect appears to be dose related with the higher dose of heroin resulting in the greater fall in heart rate.

The mean pre-drug heart rates for the dependent and the non-dependent subjects (74.1 beats/min and 62.7 beats/min respectively) were compared using a *t*-test but no significant difference was found.

Respiration rate

Although tidal volume was not measured in this study it was apparent that some subjects responded to heroin injection with a fall in tidal volume that in some cases was accompanied by a marked fall in respiration rate and in other cases not. Thus the pattern of respiration rate response to heroin varied from subject to subject. Visual inspection of the record also showed that in some dependent subjects but not non-dependent subjects the pattern of respiration was changed following heroin injection. This

Table 2 *t*-values derived from Dunnett's test for heart rate, respiration rate, blood pressure and body temperature following drug injection in non-dependent subjects.

Dose of heroin	*Time from injection/t values*		
	10 min	*1 h*	*2 h*
Heart rate			
Placebo	1.21	0.85	1.04
2.5 mg	0.52	3.99**	3.63**
5.0 mg	0.40	4.02**	4.52**
Respiration rate			
Placebo	1.33	0.33	2.10
2.5 mg	3.52**	2.17	2.39*
5.0 mg	3.39*	2.71*	3.41**
Systolic BP			
Placebo	0.92	2.93**	3.43**
2.5 mg	1.56	1.02	0.52
5.0 mg	0.15	0.15	0.79
Diastolic BP			
Placebo	1.01	2.01	0.64
2.5 mg	1.53	0.31	0.92
5.0 mg	0.37	1.65	3.96**
Body temperature			
Placebo	1.33	0.33	2.10
2.5 mg	0.68	2.03	2.64*
5.0 mg	0.84	3.78**	4.12**

*$P<0.05$; **$P<0.01$.

Table 3 F ratios derived from analyses of variance for heart rate, respiration rate, blood pressure and body temperature at all post-drug times and all doses for dependent subjects.

	Time since injection	*Dose of heroin*	*Time/dose interaction*
Heart rate	37.32**	0.63	0.30
Respiration rate	0.84	2.14	2.22
Systolic BP	19.51**	1.08	0.58
Diastolic BP	1.23	0.71	0.22
Body temperature	35.60**	1.41	3.07*

**$P<0.01$, $P<0.05$.

Table 4 F ratios derived from analyses of variance for heart rate, respiration rate, blood pressure and body temperature at all post-drug times and all heroin doses for non-dependent subjects.

	Time since injection	*Dose of heroin*	*Time/dose interaction*
Heart rate	10.25*	9.64	4.10
Respiration rate	1.44	0.03	1.66
Systolic BP	5.36*	4.55	0.06
Diastolic BP	3.05	6.71	0.56
Body temperature	3.63	0.47	0.54

*$P<0.05$.

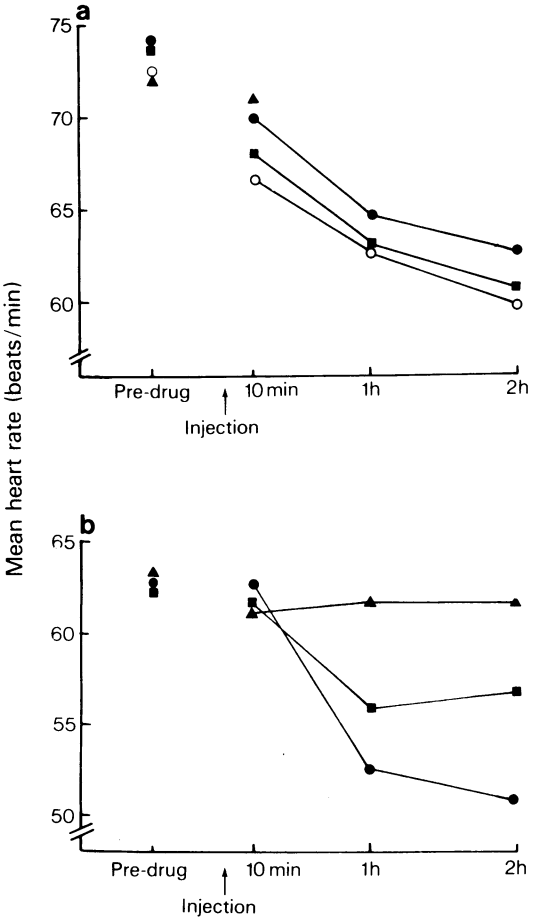

Figure 1 (a) Mean heart rate before and after intravenous saline placebo (▲) and heroin (1/6 (■) 1/3 (○) and ½ (●) of total daily opiate prescription) in all dependent subjects. Post-placebo heart-rate was available at 10 min after injection only as dependent subjects were unable to tolerate an inactive injection for more than 40 min.
(b) Mean heart rate before and after intravenous saline placebo (▲) and 2.5 mg (■) and 5 mg (●) heroin in the non-dependent subjects.

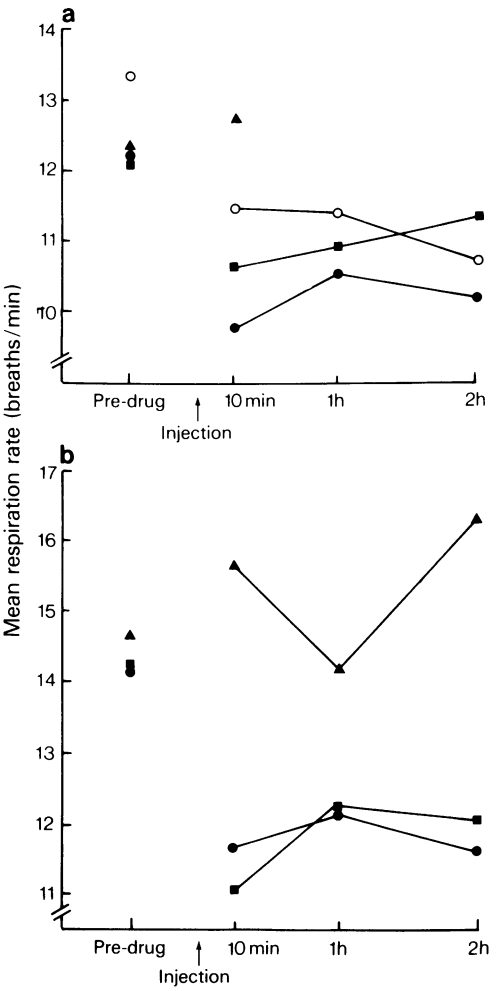

Figure 2 (a) Mean respiration rate before and after intravenous saline placebo (▲) and heroin (1/6 (■) 1/3 (○) and ½ (●) of total daily opiate prescription) in all dependent subjects.
(b) Mean respiration rate before and after intravenous saline placebo (▲) and 2.5 mg (■) and 5 mg (●) heroin in the non-dependent subjects.

pattern changed from the regular inspiration/expiration cycle usually observed to a coupled pattern of two inspiration/expiration cycles followed by a period of apnea lasting several seconds. This pattern seemed to coincide with the period immediately following injection during which dependent subjects were 'gauching' or 'nodding'—they appeared drowsy and were noticeably slow to respond when addressed by the experimenters.

The results for the dependent group showed an initial fall in respiration rate post-drug with no further change in rate over time except for 1/6 dose in which there was a return to pre-drug level at 2 h post-drug. The results for the non-dependent group showed falls in respiration rate post-heroin injection but with no effects of time or dose. Comparison of the pre-drug respiration rates from the dependent and non-dependent subjects showed no significant difference.

Blood pressure

The dependent group showed a fall in systolic blood pressure following all doses of heroin with a continuing fall over time. In contrast very little change was

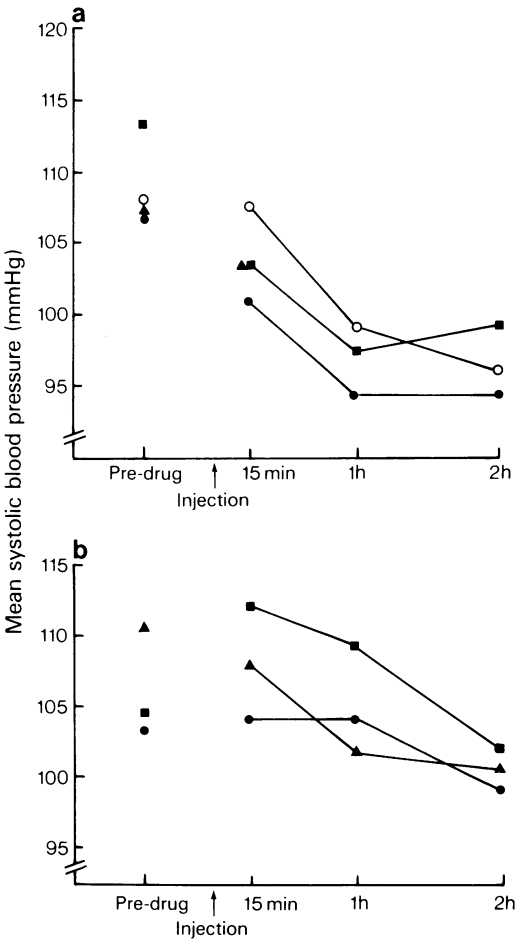

Figure 3 (a) Mean systolic blood pressure before and after intravenous saline placebo (▲) and heroin (1/6) (■) 1/3 (○) and ½ (●) of total daily opiate prescription in all dependent subjects.
(b) Mean systolic blood pressure before and after intravenous saline placebo (▲) and 2.5 mg (■) and 5 mg (●) heroin in the non-dependent subjects.

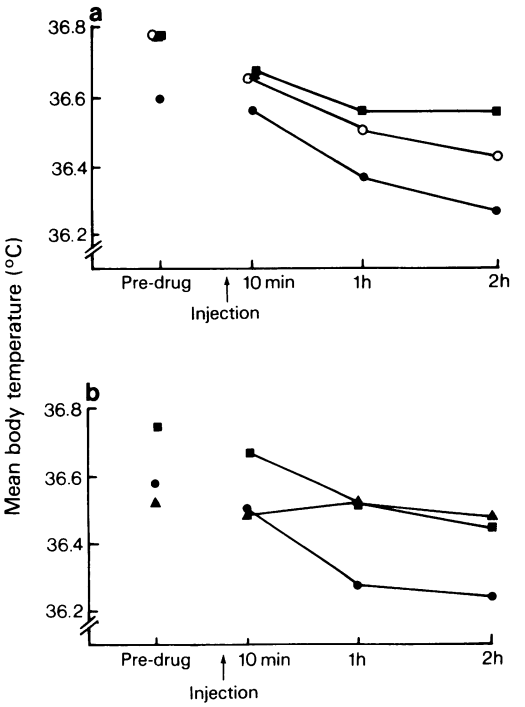

Figure 4 (a) Mean body temperature before and after intravenous saline placebo (▲) and heroin (1/6) (■) 1/3 (○) and ½ (●) of total daily opiate prescription) in all dependent subjects.
(b) Mean body temperature before and after intravenous saline placebo (▲) and 2.5 (■) and 5 mg (●) heroin in the non-dependent subjects.

seen in diastolic blood pressure except at the highest dose where a sustained fall in pressure was shown.

The non-dependent group showed no change in systolic pressure except with placebo where a fall over time was seen. This group again showed very little effect in diastolic pressure except for a fall at the higher dose of heroin 2 h after injection. There was no significant difference between the pre-drug and post-drug pressures for the dependent and non-dependent groups.

Body temperature

The results of the body temperature showed that body temperature fell after injections of heroin but not after placebo. The dependent group showed falls in body temperature at 1 and 2 h after injection with a significant time/dose interaction. The non-dependent group showed falls in body temperature at 1 and 2 h for the 5 mg dose but only at 2 h for the 2.5 mg dose. There was no significant difference between the pre-drug temperature for the dependent and non-dependent groups.

Skin temperature

Preliminary examination of the skin temperature data suggested that the pre-drug measures were rising with time. This was different from the pre-drug measures for heart rate, respiration rate and body temperature in which there was no evidence for consistent pre-drug changes. This suggested that any rise in skin temperature post-drug may just reflect a rising base level for the measure. Thus it was necessary to take into account both pre-drug levels in the analysis of the data.

The mean skin temperature for each dose of drug and at each time interval for the dependent subjects are shown in Table 5a. Analyses of variance showed

significant time effects for placebo 1/6 daily dose and 1/3 daily dose of heroin but not for the ½ daily dose. The Newman-Keuls procedure (Winer, 1971) was used to compare skin temperatures before and after injection. For placebo injection the 10 min pre- and the 10 min post-injection measurements were not significantly different from each other but were significantly different from the 30 min pre-injection measurements ($P<0.01$). This means that there was no further rise in skin temperature after placebo injection. For the 1/6 daily dose of heroin although the two pre-drug measurements were not significantly different from each other the post-drug measurements were significantly different from the 10 min pre-drug measures ($P<0.05$). The differences between the post-drug measurements and the 30 min pre-drug measurement just failed to reach significance. Thus a rise in skin temperature post-drug may be inferred. For the 1/3 daily dose there was a rising base level pre-drug and although the two pre-drug measurements were not significantly different, the post-drug measures were only significantly different from the 30 min pre-drug measures ($P<0.05$) and not the 10 min, pre-drug measurements. Thus, although there may have been a rise in skin temperature post-drug, any effect was masked by a rising pre-drug level. With the ½ daily uose group there was again a rising base level the only significant difference found was between the 30 min pre-drug level and the 10 min, post-drug level ($P<0.05$). In view of the ambiguity in interpreting these results it was decided to do no further analysis.

The results for the non-dependent subjects are shown in Table 5b. Analyses of variance were carried out for placebo and 2.5 mg and 5 mg of heroin and no significant time effects were found.

Skin conductance level

The results for the skin conductance level measures are shown in Table 6a and b. Again there appeared to be a rising base level, in the dependent group at least, before injection and so both pre-drug levels were

Table 5 (a) Mean skin temperature (°C) for dependent subjects before and after intravenous injections of heroin and placebo. *n* = number of subjects. ANOVA = Analysis of variance results.

		Pre-drug		*Post-drug*			*ANOVA*	
n	*Dose of heroin*	*30 min*	*10 min*	*10 min*	*1 h*	*2 h*	*F*	P
17	Placebo	31.21	32.51	32.48	—	—	8.46	0.001
18	1/6 daily dose	31.64	31.35	32.76	32.89	32.86	4.27	0.004
17	1/3 daily dose	33.24	33.76	34.37	34.46	34.20	4.01	0.006
17	½ daily dose	32.10	32.75	33.44	33.03	33.07	2.27	0.05

(b) Mean skin temperature (°C) for non-dependent subjects before and after intravenous injections of heroin and placebo.

4	Placebo	31.53	32.16	31.61	31.72	31.58	0.19	>0.05
4	2.5 mg	31.56	31.74	32.69	33.06	32.95	1.77	>0.05
4	5.0 mg	31.50	31.72	33.54	33.31	33.12	2.76	>0.05

Table 6 (a) Mean skin conductance levels (μmho) for dependent subjects before and after intravenous injections of heroin and placebo. *n* = number of subjects. ANOVA = Analysis of variance results.

		Pre-drug		*Post-drug*			*ANOVA*	
n	*Dose of heroin*	*30 min*	*10 min*	*10 min*	*1 h*	*2 h*	*F*	P
17	Placebo	20.62	22.76	25.87	—	—	2.86	>0.05
18	1/6 daily dose	22.60	26.89	25.50	27.44	30.64	1.89	>0.05
16	1/3 daily dose	24.16	25.20	25.71	28.86	28.85	1.37	>0.05
18	½ daily dose	20.84	26.32	24.71	27.62	28.93	3.64	0.01

(b) Mean skin conductance levels (μmho) for non-dependent subjects before and after intravenous injections of heroin and placebo.

4	Placebo	20.44	17.39	17.15	18.41	17.64	0.36	>0.05
4	2.5 mg	33.48	32.03	26.23	32.05	38.48	0.98	>0.05
4	5.0 mg	15.10	13.97	16.00	17.80	16.20	0.87	>0.05

used in the analyses. Analyses of variance carried out on the data from the dependent subjects failed to show significant time effects for placebo and all doses of heroin except for the ½ daily dose of heroin where a significant time effect was found. In this case the Newman-Keuls procedure showed that for the ½ daily dose of heroin the 1 h and the 2 h levels were significantly different from the 30 min pre-drug level only. Thus it seems that heroin did not affect skin conductance levels in the dependent subjects.

Similarly, the results for the non-dependent subjects (see Table 6b) show no effect of either placebo or heroin on skin conductance levels. Analyses of variance showed no significant effect for either dose of heroin or for placebo.

Dependent subject sub-groups

Comparisons were made between the high dose group of dependent subjects (prescribed 70 mg or more opiates per day) and the low dose group (prescribed 65 mg or less opiates per day). Analyses of variance were carried out on the data post-heroin injection at all doses. No significant differences were found between groups for heart rate, respiration rate, blood pressure nor body temperature. Pre-drug measures were also compared using a *t*-test and again no significant differences were found between groups for drug measures.

Comparisons were also made between the dependent group prescribed heroin alone and those prescribed heroin and oral methadone. Again analyses of variance failed to show any group differences for any measure post-drug and *t*-tests failed to show any group differences for pre-drug measures.

Discussion

This study has demonstrated the changes in heart rate, respiration rate, blood pressure and body temperature following intravenous injections of heroin and placebo in heroin dependent and non-dependent subjects. The results are in general agreement with the conclusions drawn by Eckenhoff & Oech in their 1960 review paper in that heroin (like morphine) results in a small decrease in respiration rate and blood pressure but also shows decreases in heart rate and body temperature. In order to demonstrate that tolerance has occurred to the effects of heroin on any of these measurements it is necessary to compare the magnitude and time course of any change across groups as described by Tress & El-Sobky (1979). Two kinds of evidence for tolerance to the effects of heroin on pupil measurements were found by these authors. Firstly, the non-dependent group and the dependent group showed similar changes in pupil diameter with heroin injection despite the fact that the latter group were receiving much larger doses of heroin. Also when high dose dependent subjects were compared with low dose dependent subjects similar changes in pupil diameter were observed despite large differences in the dose of drug administered. Secondly, the dependent group of subjects showed much faster recovery of pupil diameter than the non-dependent group. As the analysis used for the results presented here was the same as for those presented by Tress & El-Sobky (1979) the same criteria can be applied.

The heart rate measurements showed a progressive fall after heroin in both dependent and non-dependent groups with a similar fall at 2 h for the former group following all heroin doses and the latter group following 5 mg heroin (12.2, 13.1 and 10.6 beats/min for dependent subjects and 11.9 beats/min for non-dependent subjects). This fall in heart rate was an effect of the heroin injection as saline placebo failed to reduce heart rate in either subject group. However the time course of the fall in heart rate following heroin injection was quite different in the two subject groups. The non-dependent subjects only showed a significant change in heart rate from the pre-drug level at 1 h and 2 h whereas the dependent subjects showed a difference at 10 min as well as 1 h and 2 h. This effect was not dose-related in either group and, taken with the fact that the heart rate continued to fall throughout the session, this suggests that the fall in heart rate was not a direct effect of heroin on the cardiovascular system but due to an indirect, sedative effect of the heroin dose. The dependent subjects, being habituated to the effects of heroin, might be expected to respond immediately to the sedative effects of heroin whereas the non-dependent subjects perhaps being anxious about the possible effects of heroin might be slower to respond. Comparison of the low dose and high dose groups of dependent subjects also showed no differences in magnitude or time course for heart rate. This, taken with the results from the non-dependent subjects, may be taken as evidence for tolerance to the effect of heroin on heart rate. However as the effect on heart rate seems to be indirect other factors than tolerance may be involved.

The respiration rate measures showed a fall immediately after heroin injection which was maintained for 2 h in the non-dependent group and in the dependent group for the higher doses of heroin. At the lowest dose of heroin the respiration rate recovered after 2 h in the dependent group. In comparison with the dependent group the non-dependent group showed a larger fall in respiration rate at 10 min after heroin injection (3.15 and 2.58 breaths/min in the non-dependent group and 1.32, 1.99 and 2.44 breaths/min in the dependent group) despite the fact that the doses used for the dependent group were much larger than for the non-dependent group. Thus there is evidence for tolerance to the respiratory effects of heroin in that this group shows a smaller

response and faster recovery than the non-dependent group. This evidence is supported by the fact that there is no difference between the high dose and low dose dependent groups in magnitude and time course of the respiration response despite the much higher doses used in the former group.

The blood pressure measurements in the non-dependent subjects show that heroin does not affect systolic blood pressures. In fact the only significant effects shown for systolic blood pressure were with saline placebo which resulted in a fall in systolic blood pressure which continued throughout the test session. The dependent subjects showed this effect i.e. the fall in systolic blood pressure following all heroin doses. However, in view of the fact that placebo injection in the non-dependent subjects resulted in a similar fall in systolic blood pressure this effect could not be ascribed to a specific effect of heroin and was probably due to factors such as relief of anxiety or stress by the injection.

A fall in diastolic blood pressure following heroin injection occurred only at the highest doses—the ½ daily dose for the dependent group and 5 mg for the non-dependent group. However the pattern was different for the two groups, the dependent group showing a small (4.3–5.5 mmHg) fall after injection which was maintained throughout the session and the non-dependent group showing a steady fall throughout the session (0.8, 3.5, 8.0 mm at 15 min, 1 h and 2 h respectively). This suggested that, at least in the case of the non-dependent subjects the fall in diastolic blood pressure was due to non-specific sedative effects of heroin. However Drew, Dripps & Comroe (1946) found that morphine increases the likelihood of fainting on a 75° tilt in volunteers so the fall in diastolic blood pressure noted here may be direct effect of heroin on the cardiovascular system.

The fall in body temperature after heroin followed a slower time course than for the other measurements. This was to be expected in that it seems to take time for a human body to cool at room temperature. The changes recorded in body temperature at 2 h after heroin injection were small (non-dependent subjects: 0.29 and 0.33 for the 2.5 and 5 mg doses, dependent subjects: 0.2, 0.34 and 0.33°C for the 1/6, 1/3 and ½ daily prescription doses) but lay within the same range for dependent and non-dependent subjects. The fall in body temperature was not accompanied by any changes in skin conductance level or skin temperature in the non-dependent subjects and skin temperature was only affected at low dose levels in the dependent subjects. Thus the fall in body temperature was not caused by increased sweating or increased skin blood flow but neither did decreased sweating and decreased skin blood flow occur which might have reversed the fall. This body temperature change recorded in both dependent and non-dependent subjects, can be seen as a failure of the normal thermoregulatory mechanisms. Whether this might be central or a peripheral effect of the heroin is not clear.

The present authors (Tress & El-Sobky, 1979) showed that pupil diameter measurements were affected by prior ingestion of methadone in subjects prescribed both heroin and methadone. In this report no effect of prior ingestion of methadone was found for any of the measures. Again the change in pupil diameter was related to the experimental dose of heroin but in this report many of the measures showed no strong relationship to the dose of heroin. This may reflect the more variable nature of the measurements used in this study. The variation between subjects was large and may have masked subtle differences due to drug dose and ingestion of methadone. This means that of all the measurements used in this study the pupil diameter seems to have been the most productive of information about reactions to opiate drugs in dependent and the non-dependent subjects.

In conclusion it can be said that both dependent and non-dependent subjects showed similar changes in magnitude of respiration rate, heart rate, blood pressure and body temperature and that neither group showed changes in skin temperature or conductance. Where the dependent subjects differed from the non-dependent subjects was in the time course of their responses.

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