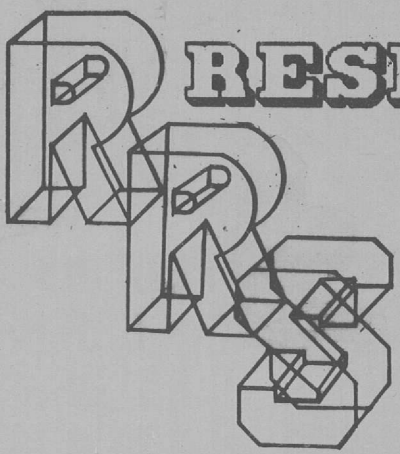

RESEARCH REPORT SERIES

17

Determination of Naltrexone Dosage for Narcotic Agonist Blockade in Detoxified Asian Addicts

Pusat Penyelidikan Dadah dan Ubat-Ubatan
(Centre for Drug Research)
U.N./W.H.O. Research and Training Centre
Universiti Sains Malaysia
Penang, MALAYSIA

RESEARCH REPORT

DETERMINATION OF NALTREXONE DOSAGE FOR NARCOTIC AGONIST BLOCKADE IN DETOXIFIED ASIAN ADDICTS

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1988

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RINGKASAN

Kekurangan pusat-pusat pemulihan dan keupayaan yang terhad program pemulihan kerajaan Malaysia menyebabkan kegunaan ubat naltrekson dicadangkan sebagai satu cara yang boleh digunakan untuk mengurangkan beban pusat-pusat pemulihan. Tujuan kajian ini adalah untuk menentukan adakah dos naltrekson yang digunakan oleh pihak Amerika Syarikat terjamin dari sudut keselamatan dan kekesanan untuk penagih-penagih dadah di Malaysia, memandangkan corak kegunaan dadah di kalangan penduduk berbilang kaum adalah berbeda berbanding dengan mereka yang di Amerika Syarikat. Tiga ratus lima puluh milligram ubat naltrekson hidroklorida (Trexon ^{TM}) diberikan untuk tempoh seminggu mengikut program berikut iaitu 100 mg pada hari pertama dan ketiga dan 150 mg pada hari kelima. Penagih-penagih dadah berbilang bangsa yang berketurunan Cina, India dan Melayu diuji dengan menggunakan ubat naltrekson. Pada hujung minggu selepas ubat naltrekson diberikan, pesakit-pewakit tersebut disuntik dengan 25 mg heroin atau placebo pada jam 12, 24, 48 dan 72 selepas dos naltrekson yang terakhir. Ini dijalankan untuk menentukan darjah dan tempoh masa naltrekson dapat menghalang kesan-kesan narkotik heroin. Penentuan dibuat dengan menggunakan kriteria fisiologik dan juga gerakbalas subjektif pesakit tersebut.

Parameter fisiologik yang dinilai ialah tekanan darah, kadar denyutan jantung, kadar pernafasan dan saiz anak mata. Perbezaan di antara parameter tersebut sebelum dan selepas suntikan heroin atau placebo digunakan sebagai penilaian keberkesanan naltrekson. Naltrekson dapat menghalang semua gerakbalas fisiologik oleh kerana kandungan heroin kecuali gerakbalas anak mata. Naltrekson masih berkesan pada masa 12 dan 24 jam selepas dos naltrekson tetapi tidak berkesan pada masa 48 dan 72 jam selepas dos naltrekson. Walau bagaimanapun gerakbalas anak mata adalah gerakbalas yang kurang penting sebagai penilaian keberkesanan naltrekson.

Penilaian saikologik menunjukkan bahawa naltrekson dapat menghalang kesan-kesan narkotik selama 48 jam. Kedua-dua bentuk penilaian iaitu fisiologik dan saikologik menunjukkan bahawa tidak ada perbezaan di antara kaum penagih-penagih dadah yang berbilang bangsa.

Hasil kajian membuktikan bahawa program dos yang dicadangkan iaitu 100 mg naltrekson untuk selama 48 jam adalah sesuai tetapi dos 150 mg untuk 72 jam tidak begitu berkesan untuk tempoh 12-14 jam di akhiran tempoh masa tersebut.

Pendapat yang dihasilkan oleh kajian ini ialah untuk kegunaan masyarakat penagih-penagih dadah di Malaysia, toleransi kepada heroin amat tinggi dan program dos 100 mg untuk rawatan tiap-tiap dua hari dan 200 gm untuk tiap-tiap tiga hari dicadangkan.

SUMMARY

The demand for rehabilitation of drug dependents outstrips the capacity of the Malaysian Government's rehabilitation programme and the use of opiate antagonist like Naltrexone may offer another solution to existing treatment. The objective of the above study was to verify whether the currently American approved dose of naltrexone provided a safe and effective blockade of narcotic effects in an adult, Malaysian population especially since the drug pattern of narcotic use and ethnic groups are different between the American and Malaysian populations. Three hundred milligrams of naltrexone hydrochloride (Trexan™) was administered per week in the form of 100 mg on Day 1, 100 mg on Day 3 and 150 mg on Day 5. The drug dependents comprise of Chinese, Malay and Indian ethnic groups. At the end of one week of naltrexone, challenge doses of 25 mg of intravenous heroin, or placebo were administered at 12, 24, 48 and 72 hours after the last naltrexone dose. This was done to verify the degree and duration of narcotic antagonism by naltrexone and assessment was based on physiological/objective criteria and subjective patient response.

Physiological assessment parameters included blood pressure, heart rate, respiratory rate and pupillometry. The postinjection values-preinjection values of the parameters at different challenge times were used as a measure of the effectiveness of naltrexone. Naltrexone adequately blocked the opiate effects on all of the above physiological responses except for pupillary miosis. Naltrexone blocked pupil response to heroin at the 12 and 24 hour challenges but not at the 48 and 72 hour challenges. However pupil response blockade is not a major finding where efficiency is concerned. Psychological assessment data showed that naltrexone was able to provide narcotic blockade for as long as 48 hours. With both physiological and psychological data, there were no significant response differences between the three ethnic groups studied.

The results show that the recommended dosage regimen of 100 mg naltrexone for 48 hours provided adequate blockade for the said period but the dosage of 150 mg for 72 hours allowed limited heroin effects for the last 12-14 hours of this period. It is therefore suggested that for the Malaysian population where heroin tolerance is relatively high the dosage regimen should consists of 100 mg every 2 days and for 3 day periods, a 200 mg dose be administered.

CHAPTER 1

1. BACKGROUND

Spencer and Navaratnam (1981) have provided a comprehensive overview of narcotic usage in East Asia in general and more recently Foong Kin and Navaratnam (1987) have reviewed in-depth for Malaysia. The latter authors report that in Malaysia, the adult drug abusers are mainly males and abusers of heroin and other opiate (e.g. morphine/opium). Most addicts identified (76.8%) were between 21 and 35 years of age, the majority (70.4%) of whom were initiated to drug use between the ages of 10 to 24 years. A significant proportion (71%) had been using drugs for periods greater than 1 year with 50.8% using it on a regular basis for a period of more than two years. On an average these drug abusers were using drugs 3-4 times a day. From this epidemiological profile, it can be inferred that they were chronic abusers.

An analysis by occupation showed that 42.5% were manual workers, 2.5% were clerical/office workers, 6.7% shopkeepers/ assistants and 25.5% unemployed. The remainder were skilled, managerial or professional workers or students. 53.1% gave influence of friends as the primary reason for initiating drug

use, with 46.7% stating pleasure, 25.3% gave curiosity as one of the reasons, whilst 14.7% stated emotional problems as one of the reasons.

Pressure of the law was the single most commonly identified reason for cessation of drug use (41.5%), pressure of families accounted for 15.4%, increase in cost was reported by 8.5% and reduced availability 10.3%. The reasons would imply that external forces seem to be the primary agent in inducing cessation of drug use which represents poor outcome prognosis. However, a smaller group stated health reasons 10.4% and well-being of their families (15.2%) as being the motivating factor to cease drug use. Obviously this group of individuals recognise that their drug dependency is affecting their jobs, health and family situation. In all probability they see their treatment as being a positive goal in enabling them to achieve self improvement. With appropriate and significant level of psychosocial support these individuals should respond positively to treatment.

The ability of drug abusers to remain in society is an important difference between abusers in Asia in general, Malaysia in particular as compared to those in Western countries. There is little evidence of a drug counterculture in Asian countries (Spencer and Navaratnam, 1981). Indeed, many addicts remain in society, retaining their jobs and maintaining family relationships. This potential strength

of family support, social and economic stability, if properly utilised, all act as positive factors towards a successful goal of drug free existence. These cultural differences make Asian drug users better candidates for management through psychosocial therapy with supportive antagonist chemotherapy.

2. DRUG TREATMENT PROGRAMS

Drug dependents, particularly opiate dependents in Malaysia have various modes of treatment currently available to them. These include traditional methods of management by "bomoh" which employ herbal medicinal teas, and spiritual and/or religious components, as well as more conventional techniques. Currently, two standardized treatment programs, outside of traditional medicine, are available. These include: in-patient withdrawal with out-patient counselling (supervised), and in-patient withdrawal and institutionalized social rehabilitation before release to supervision (aftercare). A pilot study comparing the effectiveness of these latter two treatments offered an extrapolated-tentative conclusion that social rehabilitation may have a greater success rate in maintaining the detoxified opiate dependents in an abstinent state than the other methods (Navaratnam et al., 1978).

Because of a possible greater outcome for the rehabilitated opiate dependent, the government has actively sought to improve and expand its facilities for

rehabilitation. However, to date the demand for such facilities clearly outstrips the programme capacity. Therefore, any treatment method which could (1) decrease an addict's time in rehabilitation, or (2) increase the effectiveness of the existing methods would not only improve the overall success of narcotic treatment programs but also improve the government's ability to provide effective treatment to opiate addicts.

The use of opioid antagonists may offer an adjunct to existing treatment which would provide the desired increases in effectiveness of narcotic management. According to the extinction theory, opioid antagonist treatment (Wikler, 1965) blocks the euphoric effects of opiate administration. With time the antagonism of the euphoria results in an "extinction" of opiate self-administration. The opiate dependent is then freed of his need for drugs and can fully return to society. The successful implementation of naltrexone may enable the government to return more detoxified addicts to society and at the same time ease the financial burden on the Governmental programs.

3. NALTREXONE - AN OPIOID ANTAGONIST

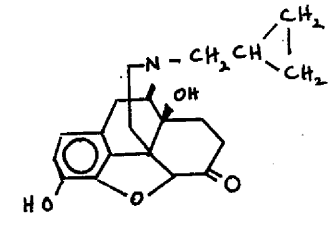
(a) Chemistry

Narcotic antagonists are normally defined as chemical compounds which block the effects of opiate

drugs. Narcotic antagonists will block the analgesia, euphoria and all physiologic changes such as pupillary constriction etc. which are produced by agonist opiates. By blocking the agonistic effects, the narcotic antagonists also prevent the development of physical dependence and tolerance to opiate drugs.

The first narcotic antagonist N-allylnorcodeine was described by Pohl in 1915, however the first clinically used antagonist was nalorphine in 1942. The limited usefulness of nalorphine led to efforts to find other drugs with narcotic antagonist activity. Cyclorphan, cyclazocine and pentazocine were subsequently developed but found to have agonist-antagonist activity.

Naltrexone hydrochloride is a white crystalline solid with a bitter taste and is an opiate antagonist with minimal agonist activity. The chemical name is 17-(cyclopropyl-methyl-)4,5-alpha-expoxy-3,14-dihydroxy-morphinan-6-one hydrochloride. Its molecular formula is $C_{20}H_{23}NO_4HCl$ and it has a pK_a of 8.13 at 37^oC.



(b) Naltrexone Pharmacology

Naltrexone was developed in response to the need for a pure narcotic antagonist with a long duration of action and minimal side effects (Archer, 1981). Naltrexone has been demonstrated to be a pure narcotic antagonist, competitively binding to the mu receptor which is responsible for the euphoric effects seen with narcotic agonists (Martin, et al., 1973). The higher affinity of naltrexone for the narcotic receptors effectively blocks the euphoric effect of narcotic agonists when administered to a previously detoxified addict (Gilman, et al., 1980). Being an antagonist, it has no effects of its own on the mu narcotic receptor and thus will not produce euphoria on binding to the narcotic receptor. However, due to the strong affinity of naltrexone for the narcotic receptors, it can displace previously bound agonists at the receptor site and produce withdrawal symptoms in nondetoxified opiate addicts (Renault, 1981). Therefore, naltrexone should only be administered to completely detoxified individuals.

(c) Naltrexone Disposition

After oral administration, naltrexone is well absorbed and reaches peak plasma concentrations within

one hour (Verebey et al., 1976). There is extensive first pass metabolism with only 5% of the dose reaching the systematic circulation unchanged. The predominant metabolic reaction is the reduction of the 6-oxo moiety of naltrexone to yield 6-beta-naltrexol in the liver. Minor metabolites include 2-hydroxy-3-o- methyl-6-beta-naltrexol and 3-o-methyl-6-beta-naltrexol. There is extensive conjugation of naltrexone and its metabolites with subsequent elimination in the urine and bile (Wall et al., 1981; Misra, 1981). The mean half- life of naltrexone has been reported to range from 7.3 to 14.7 hours (Verebey et all., 1976). The terminal half-life of the major metabolite, naltrexol, has been reported as 12.7 hours (Verebey et. al., 1976), and 7.7 hours (Wall et. al., 1981). Despite the short half-lives of naltrexone and naltrexol, the antagonism of narcotic euphoria is reported to persist up to 3 days after a 150 mg oral dose (Trexan™: An adjunct in the management of opioid addiction, Du Pont Pharmaceuticals).

(d) Naltrexone Side Effects

Clinical trials on naltrexone in the United States show that unlike previous narcotic antagonist, naltrexone has few significant adverse effects (Archer, 1981). As reported in the FDA approved package insert, the most common adverse effects included: difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and /or vomiting, low energy, joint and muscle pain, and headache. These side effects occurred in more than 10% of treated patients. Gastrointestinal complaints have been a cause for discontinuing naltrexone treatment in some patients (Kleber, et. al., 1977). Adverse effects occurring in less than 10% but more than 1% of patients include: loss of appetite, constipation, diarrhea, increased thirst, increased energy, feeling down, irritability, skin rash, delayed ejaculation, decreased potency and chills. Other side effects which occurred in less than 1% of patients included respiratory, cardiovascular and various nonspecific complaints. The most serious adverse effect reported was a dose-dependent hepatic toxicity at 300 mg per day, which is five times the recommended dosage (Trexan^{TM} package insert). This effect did not occur during treatment for opioid addiction but was reported in the studies where the

objective was to determine the effect of naltrexone on food intake in obese subjects. It is therefore recommended that all patients be monitored for signs of hepatic toxicity after initiation of therapy and at monthly intervals thereafter. A single case of idiopathic thrombocytopenic purpura has also been reported in an individual who was re-entered into naltrexone therapy (Savage et. al., 1977). The reaction may have been a hypersensitivity response to naltrexone, as it disappeared with cortisol treatment. The possibility of such hypersensitivity reactions should therefore be kept in mind during naltrexone treatment, particularly if the patient is on long term or repeated naltrexone treatment.

(e) Indicated Use for Naltrexone

Trexan^{TM} (naltrexone hydrochloride), as approved by the United States FDA, is indicated for the blockade of pharmacological effects of exogenously administered opioids as an adjunct to the maintenance of the opiate free-state in detoxified formally opioid-dependent individuals (Trexan^{TM} package insert).

(f) Naltrexone as an Adjunctive Treatment

Numerous reviews (Crabtree, 1984; Ginzburg and Glass, 1984; Greenstein et al., 1984; Renault, 1981; Resnick et al., 1979) and articles (Kleber et al,. 1977; Ling and Wesson, 1984; Martin et al., 1973, Mello et al., 1981, O'Brien et al., 1975, Washton et al., 1984) detail the development and clinical usage of naltrexone in the treatment of narcotic dependency. One thing is clear; naltrexone is not a cure and is not effective as a sole form of treatment. It does not ameliorate the underlying disorder i.e., the addiction to narcotics. It is, however, a very useful agent to prolong the cumulative time in an opiate free state in detoxified addicts in selected patient populations (Ginzburg and Glass, 1984; Ling and Wesson, 1984; Mello et al., 1981, Washton et al., 1984). Those patients likely to benefit were those with the most social and employment resources and the most conventional life styles. Thus, patients who were still in the family but whose jobs were in jeopardy had a more successful outcome than did the unemployed and "street" addict. As the Asian addict has previously been characterized as more likely to remain within society and the family, they may also benefit from naltrexone therapy.

4. RATIONALE

The theory underlying narcotic antagonist treatment of opioid dependence is based on the concept of extinction (Wikler, 1965). The assumption of this theory is that the euphoric effects of opiate administration reinforces the "drug craving". By antagonizing the euphoric effects of the narcotics the reinforcement of self-administration of narcotics is lost. With time the antagonism of the euphoria results in an "extinction" of narcotic self-administration. However, to be effective there must be total blockade of the narcotic receptors by the antagonist. Incomplete blockade in the presence of a narcotic agonist challenge will result in the manifestation of withdrawal symptoms and reinforcement of drug craving will presumably occur (Renault, 1981). It is therefore important that an appropriately high dose of the antagonist be employed which guarantees complete blockade of the receptors in the majority of patients in which it is used. Additionally, as narcotic dependency treatment is likely to be sub-chronic or chronic, the doses employed must be reasonably free from serious side effects.

In November 1984, Naltrexone (Trexan™) has been approved for the treatment of narcotic dependency in the United States. As the Malaysian population varies in several important regards from the clinically tested, American population, it is unknown whether the approved doses are effective in the Asian population.

5. Objective of Study

The objective of this study was to verify whether the currently US approved dose of naltrexone provided a safe and effective blockade of narcotic effects in an adult Malaysian male addict population, and the degree and duration of that antagonism. As the pattern of narcotic usage and the racial background of the Malaysian addict are different from his American counterpart, the currently established doses may be inappropriate in the former group. To test for racial/genetic variability, subjects will be recruited who are Chinese, Malay, or Indian. Previously detoxified subjects from each of these three racial groups will be admitted to the study. All will receive 350 mg/week Naltrexone (100 mg on Monday, 100 mg on Wednesday, 150 mg on Friday) after which assessment of antagonist effectiveness against 25 mg of intravenous heroin or placebo was assessed at 12, 24, 48 and 72 hours after the final naltrexone dose.

6. Specific Aims

The specific aim of this study is to administer 350 mg of naltrexone hydrochloride (Trexan^{TM}) per week to detoxified Malaysian male addicts (Chinese, Malay and Indian). At the end of one week of naltrexone, challenge doses of 25 mg of intravenous heroin or placebo were to be administered at selected times for up to 3 days to verify the degree and duration narcotic antagonism by naltrexone. Assessment was based upon physiological/objective criteria and subjective patient responses.

7. Significance of Study

The study will help determine whether naltrexone will provide adequate narcotic blockade of heroin in Malaysian drug addicts and also more importantly the duration of narcotic blockade. Naltrexone is the first pure antagonist to pass clinical trials with minimal serious side effects. It therefore, may be the "new method" needed to free many current ex-addicts of their opiate urge. This study has been designed to verify whether the standard naltrexone dose, as approved by the United States Food and Drug Administration, is appropriate in the Malaysian population. Upon successful completion of this study in a small group of Malaysian dependents, full scale comparative trials incorporating naltrexone with current treatments in a larger population would be initiated.

CHAPTER II

1. STUDY PROTOCOL

1.1 Subject Selection

Adult Malaysian male addicts were selected for the study. All had completed 14 days of a standard narcotic detoxification program, were free of withdrawal symptoms, gave a negative result for opiates on urinanalysis and a negative response to naloxone challenge. They were certified by a physician as being otherwise normal, with no discernable pathologies. Subjects passing these acceptance criteria were further divided into three racial groups; Chinese, Malay, Indian, with equal numbers from each racial group admitted. Subjects were matched as close as possible for other demographic backgrounds.

1.2 Subject Description

The subjects who participated in the study were all males. Fourteen were Malays, 14 Chinese and 10 Indians. All of them were between the ages of 23 to 30 years (mean 25.6 years).

All the subjects had well established histories of heroin dependence with abuse histories of 5 to 6 years (mean 5.4 years). All of them were heroin injectors who had spent about US $6.5-9 daily on drugs.

Clinically, they were classified as chronic heroin abusers. Statistically, there were no significant differences among and between the various ethnic groups in relation to age, drug abuse and social histories.

1.3 Preliminary Examinations

Upon admission to the study a complete physical, including blood and urine analysis was performed. The examination will include CBC, BUN, SGOT, SGPT, HCT, IHG, blood glucose, bilirubin albumin, urine pH, protein and glucose measurements. Any subject with a health or physical abnormality was dropped from the study. In particular, subjects had to be free of signs of hepatic dysfunction.

1.4 Study Requirements

All subjects had to complete the 14 days detoxification program and respond negatively to naloxone challenge. Subjects were stabilised for one week with naltrexone prior to heroin challenge/assessment. Plasma and urine samples were obtained from all subjects at 0 (baseline), 12, 24, 36, 48 and 72 hours after the third naltrexone dose, at which time a given subject was challenged with 25 mg of intravenous of heroin or

placebo. Subjects were blind as to the identity of the material used for the challenge and were not crossed over (i.e. a minimum of 5 subjects in each racial category received heroin, the other 5 received placebo).

Blood was obtained in heparinized vacutainer tubes by direct venipuncture and the plasma separated within 20 minutes. Plasma and urine samples were kept frozen until assay. At the time of plasma sampling physiological/objective assessments and objective patient questionnaire designed for the elucidation of withdrawal symptoms and adverse effects were administered. The physiological/objective test included blood pressure, heart rate, respiratory rate, and pupillometry.

2. STUDY DESIGN

The study design takes into account three independent variables of (1) racial or ethnic group (Chinese, Malay, Indian); (2) treatment with (heroin or placebo challenge); and (3) time of challenge (after the last naltrexone dose: 0, 2, 24, 36, 48, and 72 hours). The dependent variable was the dichotomy of complete or incomplete narcotic agonist blockade. Frequency data was collected for each cell (number of subjects exhibiting complete blockade/total number of subjects). Appropriate non-parametric tests for frequency data was utilized for

statistical analysis. The subjects in each ethnic group were randomly subdivided into two subgroups. One subgroup for each group was challenged with heroin while the other with placebo according to a double blind procedure tabled below.

Ethnic Group	Number of subjects	Time of Challenge (hour) 12	24	48	72
Group 1	7	Heroin	Heroin	Heroin	Heroin
Malays	7	Placebo	Placebo	Placebo	Placebo
Group 2	7	Heroin	Heroin	Heroin	Heroin
Chinese	7	Placebo	Placebo	Placebo	Placebo
Group 3	5	Heroin	Heroin	Heroin	Heroin
Indians	5	Placebo	Placebo	Placebo	Placebo

3. DRUG ANALYSIS

3.1 Urine Opiates

Standard tests for the determination of urine opiates as currently employed by the Drug Research Centre laboratory was used. This is a qualitative assay for the presence of various opiates and other abused drugs in the urine.

3.2 Plasma Naltrexone and 6-Beta-Naltrexol

Naltrexone and its major metabolite, 6-beta-naltrexol was determined in plasma. This assay is applicable at nanogram levels of the drug and metabolite. Plasma is extracted at pH 9 into toluene/isopropanol and then back extracted into an acidic medium. The acidic extract is assayed by reverse-phase high performance liquid chromatography (HPLC) with electrochemical detector using an octyl column.

4. ETHICAL CONSIDERATIONS

4.1 Subject Consent

A verbal or written consent was obtained from every participant in the study after adequate explanation of the object of the study and of the possible adverse effects of the drug to be utilised.

Subjects who are not available for efficacy or discontinue participation in the study prematurely for reasons unrelated to the therapy were excluded for the evaluation of efficacy.

4.2 Declaration of Helsinki/Tokyo

The investigators ensured that the criteria for clinical trials as laid down in the Declaration of the Helsinki/Tokyo were observed.

5. CLINICAL PROCEDURE

All subjects were given the recommended naltrexone dose for one week viz. 100 mg on day one and on day three and 150 mg on day five. After administration of the third dose, the subjects were challenged with either 25 mg heroin or placebo (normal saline) administered intravenously at times 12 hrs, 24 hrs, 48 hrs and 72 hrs after the administration of the third dose of naltrexone.

6. CLINICAL ASSESSMENT OF DRUG RESPONSE

Both physiological and psychological assessments were made during each drug challenge.

Psychological assessments included (i) a set of 5 self-rating questions on the effect of the heroin challenge; and (ii) the ARCI Short Form (Scales 2, 3 and 4).

Physiological assessment parameters included blood pressure, heart rate, respiratory rate and pupillometry. Blood pressure and heart rate were measured using a digital sphygmomanometer (OMRON HEM-719). The respiratory rate was assessed by observing the chest and abdominal movements of the subject. Pupillometry was performed using a Pentax-ME Super Camera with a 50-250 mm ToKina AT-X zoom lens and a Teleplus Multi-Coated 2X Tele Converter. The photographs were taken in a dark room with a Minolta 200x flashgun attachment to the camera. The subjects were allowed 4 minutes of adaptation in the dark before photographing.

With the exception of the 5 self-rating questions on the effect of the challenge injection which was administered only once, after the challenge, all the physiological assessments were made 15 minutes prior to the challenge, then at 5 minutes, 30 minutes and 60 minutes after the challenge.

In the post-trial follow-up the subjects were observed twice daily for four days after the last challenge. The signs observed were narcotic craving and for standard narcotic withdrawal symptoms. The observation was made by a physician who was blind as to the identity of the challenge substance.

7. DATA ANALYSIS

The experimental design utilised in the study was basically a split-plot three-way factorial design. Therefore the analysis of variance procedure was adopted for purposes of data analysis. Of particular interest was the significance of the effects of the substance challenge, time of challenge, ethnicity, and the interactions between and among these factors.

The statistical analysis of the data from the trial was done at the Drug Research Centre, USM, Penang, Malaysia and concurrently by the Biometrics group, Medical Research Section, DuPont Pharmaceutical and Biotechnology R & D Division, U.S.A..

CHAPTER III

1. RESULTS

1.1. Physiological Assessment

Tables 1A to 4C show the results of physiological assessments carried out in the study. Figure 1 and Table 4D show the mean change from pre-injection score for the physiological parameters in subjects receiving placebo or heroin with challenge times after last naltrexone dose. The three major factors studied here are drug treatment (with naltrexone), time of challenge (with heroin or placebo) and ethnicity. Treatment is the main factor as the blocking effects of heroin by naltrexone is important to the study. The time of challenge with heroin is also important as there may be decreased blockade when naltrexone and its metabolites plasma levels decrease with time. Any interaction between time of challenge and treatment can be correlated with plasma levels of naltrexone to give an estimate of the naltrexone levels required for narcotic blockade. The ethnicity and drug treatment factors will determine whether there are any ethnic differences in the effects of naltrexone on drug treatment.

Table 1A: Determination of blood pressure (mm/Hg) following naltrexone treatment and subsequent challenge with placebo or heroin in Malay subjects

ETHNICITY MALAY

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N01	118/86	126/68	131/45	117/17	118/62	116/58	122/50	110/50	120/50	120/56	117/48	110/45	112/46	110/44	122/45	112/46
	N02	120/68	120/64	115/50	111/64	104/68	102/62	97/52	102/57	120/60	104/56	117/44	95/47	106/60	106/56	108/53	114/54
	N07	128/68	120/68	129/56	126/59	128/72	130/64	110/52	116/56	120/64	110/70	111/51	119/51	110/58	108/48	110/43	119/48
	N11	112/60	112/64	113/61	113/61	110/61	112/68	108/50	97/49	112/68	110/80	101/48	109/55	106/58	112/64	110/44	112/54
	N12	112/63	110/68	109/61	105/56	104/54	108/50	107/45	110/49	110/60	100/60	107/49	107/56	100/54	104/56	115/50	115/59
	N16	116/72	112/76	113/61	116/60	102/62	100/68	100/54	106/57	110/80	110/70	110/59	104/46	104/64	108/60	99/56	113/62
	N17	108/70	108/70	106/65	104/71	110/65	110/65	108/59	112/54	116/72	110/62	106/54	116/54	118/62	116/68	116/65	115/46
Heroin	Patient Code																
	N4	130/65	130/70	127/56	120/58	120/70	120/60	114/59	107/70	130/60	120/70	120/63	112/58	115/70	114/74	119/68	109/66
	N5	104/62	108/64	110/63	111/59	110/70	110/68	105/58	110/64	114/68	120/78	125/67	116/43	104/64	108/68	120/66	118/51
	N6	118/52	118/64	116/62	118/58	120/68	120/62	114/57	126/52	122/60	124/64	108/43	110/45	124/60	120/60	122/56	120/56
	N8	138/80	142/84	134/76	146/78	126/65	128/70	125/82	138/84	110/70	140/80	121/82	134/75	128/76	132/80	124/74	134/76
	N9	124/52	126/68	113/46	113/52	128/68	120/60	110/44	107/44	108/52	110/60	113/53	111/47	108/56	114/64	122/48	110/44
	N10	108/68	106/70	107/65	104/68	114/66	118/68	108/60	103/62	120/78	130/84	121/57	103/61	108/66	112/78	116/58	104/63
	N15	126/64	128/68	100/48	102/53	114/62	116/65	113/55	105/44	120/80	104/60	117/61	116/55	118/64	122/70	116/50	111/50

Table 1B: Determination of blood pressure (mm/Hg) following naltrexone treatment and subsequent challenge with placebo or heroin in Chinese subjects.

ETHNICITY CHINESE

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N18	120/70	120/70	122/77	113/74	110/80	110/70	118/60	114/65	110/70	108/70	125/71	107/64	120/70	110/60	105/58	101/52
	N21	130/78	110/70	110/70	107/62	104/60	100/60	105/65	95/51	104/70	100/60	100/63	95/52	115/70	110/60	104/59	101/49
	N22	110/70	110/70	113/65	114/59	110/70	92/68	101/61	101/66	100/80	100/70	119/68	98/53	100/78	106/70	102/60	102/61
	N28	110/68	120/80	97/58	106/49	108/64	113/74	103/50	89/56	110/78	110/60	94/50	89/55	128/80	108/70	99/56	89/50
	N29	100/58	100/60	107/47	98/47	100/60	104/60	100/46	97/47	110/55	110/60	106/44	105/47	108/50	110/50	101/47	102/46
	N30	120/80	120/70	117/55	104/56	110/68	110/75	103/56	110/54	120/70	118/70	100/50	116/60	130/60	110/60	119/53	110/44
	N31	120/70	120/80	119/62	113/66	104/68	110/68	123/71	113/67	104/66	101/70	113/61	100/57	110/64	108/60	106/64	115/58
Heroin	Patient Code																
	N19	140/80	130/80	118/63	113/57	110/80	107/50	110/62	120/80	110/80	110/59	112/59	112/53	120/70	120/80	122/60	107/54
	N20	120/70	110/70	124/56	109/61	110/60	130/72	130/65	114/60	130/80	130/70	116/59	109/49	120/60	120/76	115/56	111/49
	N23	120/70	130/70	119/36	124/45	110/60	110/68	112/48	115/40	110/50	110/70	121/50	113/41	110/50	110/64	116/40	107/44
	N24	130/90	130/80	118/70	125/76	110/82	100/70	103/68	114/69	110/70	113/70	116/71	123/61	110/70	110/70	101/56	92/61
	N25	100/60	100/60	94/56	92/45	100/65	100/65	106/43	104/44	100/62	100/60	107/50	114/52	100/65	115/70	105/50	115/44
	N26	100/60	90/60	104/56	98/62	90/65	98/60	104/62	98/50	100/60	94/60	114/60	119/56	110/60	110/75	113/64	116/56
	N28	130/80	130/70	126/26	121/65	110/62	100/55	116/47	111/62	110/65	100/70	118/53	121/50	120/80	120/80	128/56	103/61

Table 1C: Determination of blood pressure (mm/Hg) following naltrexone treatment and subsequent challenge with placebo or heroin in Indian subjects

ETHNICITY INDIAN

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N32	92/41	103/57	95/47	99/47	80/41	88/40	84/39	93/36	98/52	100/52	90/45	112/47	94/48	94/50	84/51	91/50
	N35	107/55	114/64	110/52	122/74	97/62	101/61	103/56	101/58	110/70	120/74	115/53	116/44	110/70	105/60	127/54	104/63
	N36	139/55	117/42	119/53	113/48	122/59	113/53	119/50	121/42	120/70	120/70	109/43	115/50	110/70	120/68	105/50	112/48
	N39	95/56	90/64	101/62	107/72	100/64	90/70	110/53	101/53	110/50	104/68	98/48	98/43	100/70	92/72	94/53	106/52
	N41	127/60	127/62	114/53	117/53	130/70	120/74	104/58	108/50	130/80	120/80	116/52	110/55	120/65	100/70	104/50	105/50
Heroin	Patient Code																
	N33	146/79	137/65	127/75	139/61	119/71	119/69	119/71	121/65	110/70	120/70	123/67	119/71	120/80	124/80	124/74	122/71
	N34	135/71	134/83	150/50	123/46	116/68	113/85	129/65	128/70	120/82	130/80	119/62	124/65	125/88	125/80	113/79	116/75
	N37	102/59	101/59	110/58	98/47	100/60	100/54	105/48	93/50	110/70	100/70	97/48	103/56	100/60	90/60	113/60	110/52
	N38	106/65	91/56	104/59	92/67	105/70	100/64	95/54	101/56	120/72	110/70	120/59	107/64	120/70	95/60	110/70	113/71
	N40	113/65	119/68	101/65	102/73	100/70	100/70	104/56	109/70	110/70	104/64	101/61	112/66	100/70	110/80	104/61	116/71

Table 2A: Determination of heart rate (mm^{-1}) following naltrexone treatment and subsequent challenge with placebo or heroin in Malay subjects

ETHNICITY MALAY

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N1	68	64	53	52	48	50	50	49	60	56	56	63	56	58	60	56
	N2	64	58	53	52	56	54	51	49	56	62	62	62	58	56	57	54
	N7	64	66	68	60	64	62	59	58	72	66	63	62	76	76	62	69
	N11	66	62	62	59	72	68	58	60	58	64	58	65	68	64	62	64
	N12	52	52	54	47	60	58	50	52	64	60	56	55	60	62	50	59
	N16	60	56	57	56	56	56	55	56	52	52	55	57	58	64	57	57
	N17	50	48	45	43	56	58	59	57	56	56	57	53	64	58	55	53
Heroin	Patient code																
	N4	70	72	65	66	62	60	60	49	70	64	63	63	70	72	62	61
	N5	56	52	-	48	50	52	53	49	66	66	63	62	80	72	59	66
	N6	56	54	49	56	50	54	49	46	64	66	52	51	62	60	57	55
	N8	68	66	67	64	58	60	58	50	56	60	51	62	64	64	58	59
	N9	66	62	57	55	54	52	53	55	54	62	54	62	64	72	60	60
	N10	64	62	58	60	64	66	63	62	66	64	63	60	68	64	64	62
	N15	72	74	60	59	76	80	66	67	72	72	70	63	74	80	77	62

Table 2B: Determination of heart rate (mm^{-1}) following naltrexone treatment and subsequent challenge with placebo or heroin in Chinese subjects

ETHNICITY CHINESE

		TIME OF CHALLENGE														
		12 Hour				24 Hour				48 Hour				72 Hour		
			Post				Post				Post				Post	
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N18	64	64	57	55	6[illegible]	60	55	55	62	60	52	61	64	62	58	61
	N21	92	92	89	96	8[illegible]	84	91	83	90	88	89	91	84	88	85	78
	N22	72	80	76	65	7[illegible]	69	84	76	72	68	77	71	72	76	74	79
	N28	68	60	70	60	7[illegible]	65	68	72	80	72	79	71	66	70	67	66
	N29	64	68	58	60	6[illegible]	64	63	63	74	68	69	75	92	72	74	77
	N30	66	64	59	55	7[illegible]	80	78	68	84	78	86	64	80	75	78	76
	N31	52	50	60	55	6[illegible]	60	56	60	57	60	56	58	60	60	59	62
Heroin	Patient Code															
	N19	80	72	68	62	7[illegible]	68	68	75	84	90	73	76	78	72	63	57
	N20	84	88	79	78	72	80	84	82	89	94	86	89	88	90	88	90
	N23	52	52	53	51	56	54	58	56	59	58	51	53	63	60	52	45
	N24	68	72	70	65	69	64	61	59	80	68	70	61	70	76	65	70
	N25	72	64	62	66	76	80	75	68	88	76	69	84	80	72	67	65
	N26	58	50	48	48	56	58	61	57	60	52	56	56	62	66	56	58
	N27	64	64	58	49	64	64	63	58	63	64	55	63	56	63	57	56

Table 2C: Determination of heart rate (mm^{-1}) following naltrexone treatment and subsequent challenge with placebo or heroin in Indian subjects

ETHNICITY INDIAN

		TIME OF CHALLENGE														
		12 Hour				24 Hour				48 Hour				72 Hour		
			Post				Post				Post				Post	
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N32	48	52	53	47	57	53	51	52	54	54	48	57	51	54	54	43
	N35	73	76	71	56	79	71	67	66	72	80	81	76	68	66	69	74
	N36	62	59	55	59	97	70	62	63	68	70	60	61	60	66	62	66
	N39	66	68	55	59	63	66	61	64	60	62	56	55	58	56	53	54
	N41	71	59	58	53	60	56	59	47	62	60	62	50	56	60	54	57
Heroin	Patient Code															
	N33	61	59	64	59	62	60	61	54	66	64	62	60	64	75	71	72
	N34	74	88	67.5	60	82	90	69	69	66	75	64	67	63	60	58	55
	N37	65	60	59	50	57	50	64	78	57	60	58	52	60	60	50	50
	N38	73	75	74	69	63	69	70	71	62	68	70	69	70	64	75	66
	N40	56	56	60	60	57	54	54	69	62	55	47	57	52	51	44	45

Table 3A: Determination of respiratory rate (mm^{-1}) following naltrexone treatment and subsequent challenge with placebo or heroin in Malay subjects

ETHNICITY MALAY

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Treatment	Patient Code																
Placebo	N1	20	18	18	18	20	20	16	18	15	19	22	16	18	16	16	18
	N2	20	18	18	16	20	20	18	20	20	18	18	16	20	20	18	20
	N7	20	22	22	20	17	18	16	20	20	23	20	20	24	26	22	20
	N11	22	20	20	20	20	20	20	18	22	20	20	22	20	18	18	18
	N12	22	20	22	20	22	21	20	20	21	24	24	22	20	20	24	22
	N16	20	22	20	18	16	16	16	16	15	16	16	16	18	16	16	16
	N17	20	18	18	20	20	20	22	20	21	17	22	20	20	18	20	20
Heroin	Patient Code																
	N4	24	26	24	23	22	22	22	22	21	21	20	20	24	20	20	20
	N5	20	18	15	16	18	15	16	16	16	15	16	15	16	16	18	16
	N6	18	20	20	18	17	16	16	18	20	19	16	20	20	19	20	20
	N8	22	20	22	20	19	18	16	18	17	18	16	18	16	17	18	18
	N9	18	18	18	18	18	20	20	20	22	19	18	18	22	19	20	20
	N10	22	20	18	20	19	20	16	20	20	22	20	20	20	22	20	20
	N15	18	20	18	20	24	22	20	20	20	16	16	18	22	24	20	20

Table 3B: Determination of respiratory rate(mm^{-1}) following naltrexone treatment and subsequent challenge with placebo in Chinese subjects

ETHNICITY CHINESE

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Treatment	Patient Code																
Placebo	N18	24	22	20	20	17	14	16	14	16	15	20	16	19	14	18	20
	N21	16	24	20	21	16	18	18	18	16	18	20	15	18	18	18	20
	N22	26	26	24	22	22	22	20	20	22	24	24	20	23	20	20	25
	N28	20	16	18	18	22	17	18	20	23	14	18	20	18	18	18	18
	N29	22	22	18	18	22	24	20	18	21	20	24	20	24	22	21	22
	N30	17	15	18	18	15	16	18	16	15	15	18	20	12	12	16	18
	N31	20	17	16	15	15	18	20	20	15	18	18	21	15	14	20	18
Heroin	Patient Code																
	N19	20	20	20	20	17	17	20	20	18	18	18	20	15	12	16	12
	N20	25	20	20	20	20	20	20	20	20	18	18	18	19	16	18	12
	N23	24	17	18	17	19	17	18	17	22	18	24	24	22	18	18	18
	N24	20	18	20	20	16	18	18	12	18	17	18	20	16	12	16	20
	N25	22	20	20	20	19	17	20	20	17	15	16	20	21	21	18	20
	N26	20	16	18	15	23	24	20	20	21	19	20	20	18	13	18	15
	N27	20	18	18	20	20	15	20	18	22	20	20	22	21	15	20	20

Table 3C: Determination of respiratory rate (mm^{-1}) following naltrexone treatment and subsequent challenge with placebo or heroin in Indian subjects

ETHNICITY INDIAN

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N32	21	19	18	16	18	18	18	25	16	15	18	20	18	15	16	15
	N35	20	18	18	18	18	18	18	20	20	20	20	20	22	20	21	20
	N36	20	18	18	16	15	14	16	20	18	19	20	21	20	17	16	20
	N39	18	18	18	20	19	22	21	24	19	21	21	21	17	20	18	20
	N41	22	21	20	20	18	17	18	20	20	18	18	20	18	17	18	18
Heroin	Patient Code																
	N33	18	16	18	20	21	24	21	20	20	18	18	18	19	18	18	18
	N34	18	18	18	18	15	20	18	22	17	18	20	22	15	15	19	15
	N37	18	16	18	18	16	14	18	20	17	14	18	16	16	14	18	18
	N38	18	24	18	20	22	18	18	20	15	13	16	20	13	10	20	18
	N40	20	19	20	20	21	21	20	20	22	19	18	18	21	19	16	18

Table 4A: Determination of pupillometry (mm) following naltrexone treatment and subsequent challenge with placebo or heroin in Malay subjects

ETHNICITY MALAY

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N1	6.96	>.3	6.15	>.45	6.25	6.15	6.3	6.25	6.2	6.15	6.4	6.3	6.55	6.25	5.5	5.55
	N2	7.03	7.05	7.15	7.05	7.05	7.0	7.0	6.05	6.85	70	6.97	6.35	7.15	7.05	6.45	6.2
	N7	6.05	6.25	6.2	5.9	6.15	6.15	6.3	6.2	6.5	6.15	6.35	6.65	6.15	6.0	6.05	6.55
	N11	6.65	6.65	6.85	6.75	6.3	>.2	6.55	6.5	6.4	6.1	6.3	6.2	6.05	6.4	6.35	6.4
	N12	6.4	6.75	6.5	6.2	6.45	6.35	6.15	6.6	6.35	6.3	6.6	6.7	6.05	6.05	6.35	6.3
	N16	6.05	6.0	5.75	5.6	5.45	5.45	5.45	5.6	6.0	5.2	5.5	4.95	5.45	5.05	5.05	5.15
	N17	>.65	6.0	6.05	6.15	6.5	6.45	6.55	6.8	6.15	6.35	6.35	6.6	6.1	6.15	6.35	6.05
Heroin	Patient Code																
	N4	6.95	6.?	7.05	6.63	6.9	6.6	6.4	6.55	6.9	5.95	6.3	6.05	7.1	4.55	4.55	4.25
	N5	7.6	7.6	7.65	7.5	7.8	8.0	7.6	7.75	7.75	7.5	7.7	7.7	7.3	4.75	5.25	6.05
	N6	7.5	7.35	7.4	7.4	7.05	7.1	7.25	7.2	7.3	7.95	7.15	7.4	7.45	6.65	6.95	6.5
	N8	8.4	8.1	8.1	8.05	7.95	8.15	8.35	7.85	8.25	8.05	7.9	8.35	7.95	7.15	7.2	7.35
	N9	7.0	6.8	6.95	6.5	6.65	6.6	6.9	6.6	6.25	6.3	5.8	5.85	6.6	4.2	4.45	4.8
	N10	7.9	7.8	7.95	7.9	7.8	7.7	7.3	7.45	7.75	7.4	7.5	7.2	7.35	7.3	7.95	7.2
	N15	7.05	6.5	7.0	7.05	6.95	6.5	6.6	6.5	7.1	5.9	6.35	5.5	6.4	3.05	3.2	2.9

Table 4B: Determination of pupillometry (mm) following naltrexone treatment and subsequent challenge with placebo or heroin in Chinese subjects)

ETHNICITY CHINESE

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N18	6.5	6.3	6.3	6.6	6.0	6.7	6.2	6.7	5.9	6.8	6.7	6.5	6.5	6.3	6.4	6.5
	N21	6.35	6.6	6.4	6.7	6.1	6.4	6.5	6.0	5.9	6.0	6.0	5.9	6.3	6.2	6.2	6.7
	N22	7.6	7.8	7.6	8.0	7.5	7.6	7.3	6.9	7.7	7.4	7.4	8.0	7.4	7.0	8.1	8.0
	N28	5.95	5.7	5.8	5.4	5.7	5.7	4.7	5.4	5.0	5.2	5.0	6.0	5.2	5.8	5.7	5.9
	N29	7.1	7.0	7.1	7.0	6.3	6.8	6.2	6.4	6.4	6.5	7.0	7.2	6.9	7.1	6.6	7.0
	N30	7.05	6.1	6.3	6.1	5.9	5.5	5.8	6.0	6.0	5.8	6.5	6.9	5.0	6.3	6.0	5.9
	N31	7.3	7.7	6.6	7.0	7.1	7.5	7.4	6.6	7.1	7.8	7.5	7.2	7.0	7.7	7.4	7.2
Heroin	Patient code																
	N19	6.25	6.3	6.2	6.0	5.2	4.4	4.0	3.9	5.5	3.1	3.6	4.0	6.2	2.5	3.1	2.6
	N20	6.35	6.0	6.1	6.2	6.9	4.0	4.8	5.8	7.0	4.2	4.5	4.3	6.6	3.2	3.1	3.1
	N23	6.9	8.2	7.6	5.2	7.5	7.7	7.7	7.0	8.0	7.5	7.1	7.9	6.6	4.5	6.4	7.0
	N24	5.9	6.1	6.0	6.7	5.9	6.2	5.5	6.0	5.8	6.0	5.9	6.0	5.8	3.8	4.2	5.0
	N25	6.45	6.2	6.7	6.3	6.7	6.7	6.5	6.1	6.3	6.5	6.3	6.3	6.5	4.0	4.7	4.9
	N26	6.15	7.0	6.9	6.6	6.2	5.8	5.3	5.4	6.6	5.0	5.5	5.2	6.8	3.6	4.1	3.8
	N27	6.9	6.5	6.7	6.6	6.3	6.2	6.0	6.1	7.0	6.5	6.4	6.5	6.8	4.5	4.3	5.0

Table 4C: Determination of pupillometry (mm) following naltrexone treatment and subsequent challenge with placebo or heroin in Indian subjects

ETHNICITY INDIAN

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
			Post				Post				Post				Post		
Treatment	Patient Code	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Placebo	N32	8.0	8.0	7.2	7.3	7.6	6.7	7.2	7.2	7.0	6.9	6.8	6.8	7.2	6.1	7.2	7.0
	N35	6.0	6.0	5.8	5.8	6.0	6.1	5.8	5.4	5.7	5.5	5.9	6.1	5.5	5.9	5.6	5.0
	N36	6.2	6.8	6.4	6.6	6.6	6.3	6.5	6.1	6.6	6.0	6.2	6.1	6.0	6.3	6.2	6.0
	N39	5.5	6.7	6.4	6.2	6.6	6.1	6.9	6.4	6.1	6.6	6.8	6.8	6.1	6.3	6.5	7.0
	N41	6.1	6.0	6.0	6.1	5.9	5.3	5.9	5.4	5.2	5.8	5.9	6.0	5.7	5.5	5.8	5.6
Heroin	Patient code																
	N33	6.5	6.6	6.7	6.7	6.9	6.3	6.3	6.3	5.6	6.1	6.2	6.2	6.6	3.0	5.5	4.2
	N34	6.8	5.8	5.9	6.1	6.0	5.7	5.7	6.5	5.6	5.3	4.5	5.2	5.9	4.5	4.2	4.6
	N37	6.2	6.4	6.5	6.6	6.8	6.6	6.7	6.6	6.4	5.9	6.3	6.3	6.0	5.0	5.0	5.2
	N38	6.3	5.6	6.2	6.5	6.4	3.6	4.0	3.6	6.2	2.5	5.2	2.9	6.6	3.4	3.1	3.1
	N40	6.2	6.1	6.2	6.1	6.3	6.0	6.0	6.1	5.8	5.3	5.9	6.1	6.2	4.0	4.5	4.9

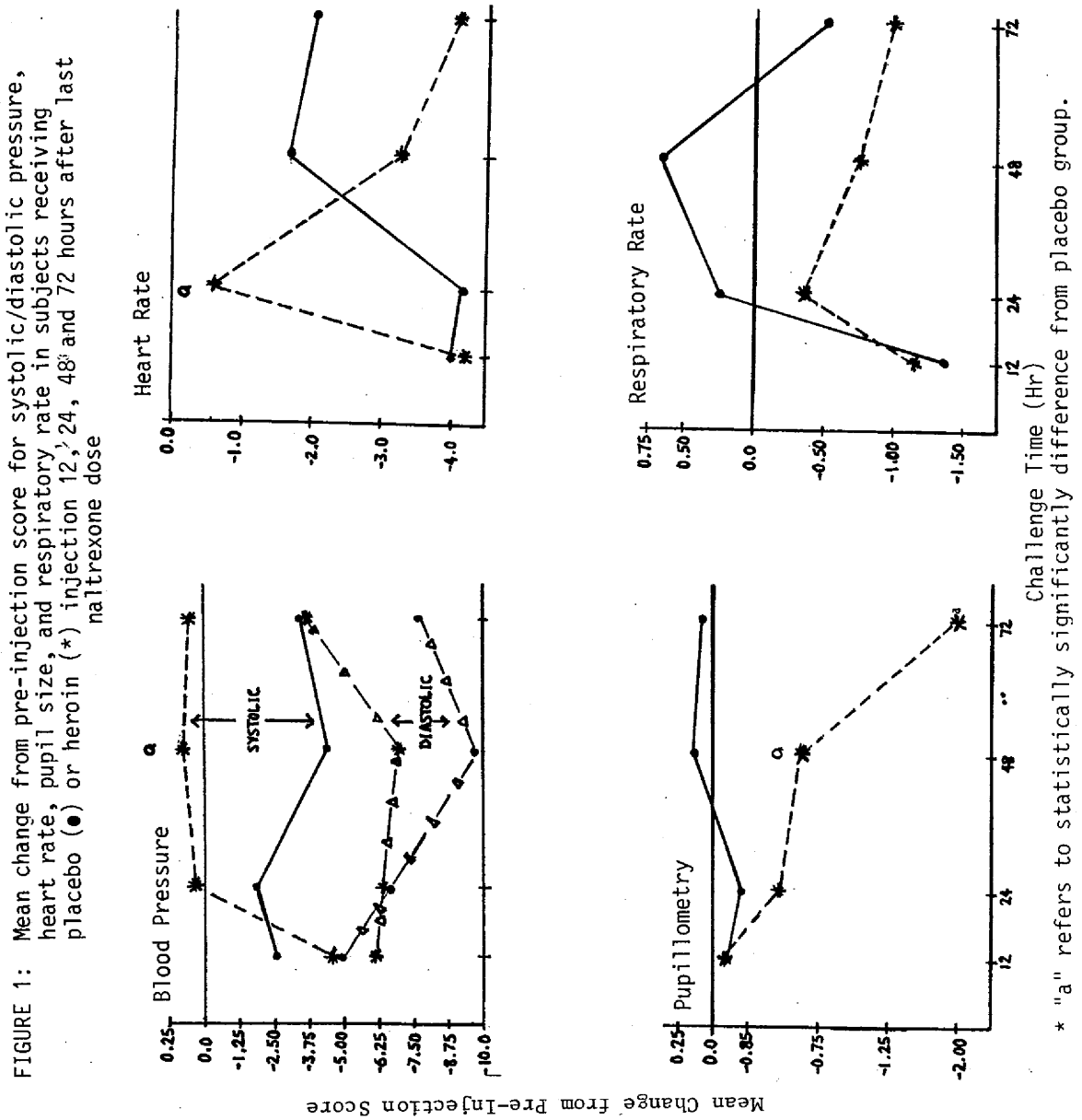


FIGURE 1: Mean change from pre-injection score for systolic/diastolic pressure, heart rate, pupil size, and respiratory rate in subjects receiving placebo (●) or heroin (*) injection 12, 24, 48 and 72 hours after last naltrexone dose

* "a" refers to statistically significantly difference from placebo group.

TABLE 4D

The Mean Difference Scores * (S.E.M.) For The Five Physiological Parameters

PHYSIOLOGICAL PARAMETERS	CHALLENGE TIMES (HRS)			
	12	24	48	72
Systolic BP				
Placebo	-2.60(1.86)	-1.80(1.64)	-4.41(1.44)	-3.48(2.28)
Heroin	-4.53(1.50)	0.33(1.53)	0.76(2.07)	0.48(1.58)
Diastolic BP				
Placebo	-4.95(2.69)	-6.62(0.98)	-9.74(1.68)	-7.75(1.44)
Heroin	-6.14(1.98)	-6.51(1.82)	-7.08(2.01)	-3.63(1.08)
Heart Rate				
Placebo	-3.96(1.07)	-4.16(1.92)	-1.65(1.02)	-2.03(1.20)
Heroin	-4.23(0.95)	-0.58(1.10)	-3.28(1.23)	-4.11(1.34)
Pupillometry				
Placebo	-0.09(0.09)	-0.19(0.13)	0.14(0.09)	0.08(0.10)
Heroin	-0.07(0.07)	-0.47(0.17)	-0.65(0.21)	-1.97(0.25)
Respiration				
Placebo	-1.37(0.51)	0.23(0.47)	0.64(0.54)	-0.51(0.41)
Heroin	-1.18(0.53)	-0.35(0.47)	-0.73(0.42)	-1.03(0.48)

* Average Post-Injection Value - Pre-Injection Value

S.E.M. - Standard Error of Mean

To measure the effects of drug treatment, time of challenge and race, the differences between the values obtained before drug injection and the mean value of the three measurements after the drug injection (i.e. at times 5, 30 and 60 min) were calculated for each subject at each drug challenge (i.e. 12, 24, 48 and 72 hr). An analysis of variance procedure appropriate for the study design was then used to analyse the data based on the differences obtained. This was a statistical computer programme called ANOVA. The results of these analyses are presented in Tables 5 to 12.

i. Systolic Blood Pressure

Results of the analysis of systolic blood pressure are presented in Table 5. The main effects of ethnicity, drug treatment with heroin or placebo and time of challenge alone were not significant. Significant differences however were obtained with two interactions. The first interaction is between ethnicity or race and time but since this interaction is not related to heroin or placebo administration, it can be ignored. The second significant interaction is between drug treatment with heroin or placebo and time. This interaction was further

TABLE 5

ANOVA TABLE FOR SYSTOLIC BLOOD PRESSURE

Source of Variation	SS	df	MS	F	P
A	23.756	2	11.878	0.115	NS
B	170.75	1	170.75	1.655	NS
AXB	59.11	2	29.555	0.286	NS
Error	3299.607	32	103.112	-	-
C	117.877	3	39.292	0.979	NS
AXC	635.714	6	105.952	2.64	0.02
BXC	350.268	3	116.756	2.909	0.037
AXBXC	187.731	6	31.288	0.779	NS
Error	3852.239	96	40.127	-	-

A = Ethnicity B = Treatment C = Challenge Time

analysed to see when the interaction is significant (Table 7). Time of challenge effects were significant for the heroin treated group and were significant only at the 48 hour challenge. It was therefore expected to find these significant drug treatment effects at 72 hours if there is significance at 48 hrs but this was not observed. Therefore the significant drug treatment effects at the 48 hour challenge may be just an artefact.

Table 6 shows the results of the analysis for diastolic blood pressure. There were significant effects of time on diastolic blood pressure while all the other factors and interactions were not significant. However, since the significant difference observed in relation to time alone is independent of the other factors, this difference is not important.

ii. Heart Rate

Table 8 shows the results of the analysis for heart rate. All the main effects were not significant and only the interaction between drug treatment and time of challenge was significant. This interaction was further analysed and treatment effects at the 24 hr challenge were significant (Table 9). This was unexpected and the significance could be an artefact.

TABLE 6

ANOVA TABLE FOR DIASTOLIC BLOOD PRESSURE

Source of Variation	SS	df	MS	F	P
A	360.273	2	180.136	2.899	NS
B	92.828	1	92.828	1.494	NS
AXB	57.34	2	28.670	0.461	NS
Error	1988.145	32	62.129	-	-
C	454.664	3	151.554	4.083	0.009
AXC	457.116	6	76.186	2.052	0.02
BXC	227.626	3	75.875	2.044	NS
AXBXC	221.585	6	36.93	0.995	NS
Error	3563.119	96	37.115	-	-

A = Ethnicity B = Treatment C = Challenge Time

TABLE 7

ANOVA TABLE FOR BC INTERACTIONS

(Sytolic Blood Pressure)

Source of Variation	SS	df	MS	F	P
C at b_1	97.8538	3	32.6179	0.8128	NS
C at b_2	379.06	3	126.353	3.148	$P < 0.05$
Error	3852.239	96	40.127	-	-
B at c_1	72.284	1	72.284	1.2937	NS
B at c_2	33.464	1	33.464	0.5989	NS
B at c_3	284.303	1	284.303	5.0884	$P < 0.05$
B at c_4	148.02	1	148.02	2.6492	NS
Error	7151.776	128	55.873	-	-

B = Treatment C = Challenge Time

TABLE 8

ANOVA TABLE FOR HEART RATE

Source of Variation	SS	df	MS	F	P
A	17.215	2	8.607	0.251	NS
B	1.849	1	1.849	0.054	NS
AXB	194.9	2	97.45	2.849	NS
Error	1094.296	32	34.196	-	-
C	64.391	3	21.463	0.778	NS
AXC	274.832	6	45.805	1.66	NS
BXC	237.508	3	79.169	2.869	0.039
AXBXC	170.576	6	28.429	1.03	NS
Error	2648.237	96	27.585	-	-

A = Ethnicity B = Treatment C = Challenge Time

TABLE 9

ANOVA TABLE FOR BC INTERACTIONS

Heart rate

Source of Variation	SS	df	MS	F	P
C at b_1	95.9785	3	31.9928	1.1598	NS
C at b_2	164.4526	3	54.8175	1.98722	NS
Error	2648.237	96	27.585	-	-
B at c_1	0.6429	1	0.6429	0.0219	NS
B at c_2	121.756	1	121.756	4.1643	$P < 0.05$
B at c_3	25.291	1	25.291	0.8650	NS
B at c_4	41.3925	1	41.3925	1.4154	NS
Error	3742.464	128	29.238	-	-

B = Treatment C = Challenge Time

Alternatively, this could be due to accumulation of the heroin levels following administration at 12 hours leading to excessive levels of heroin/morphine. The appearance of significance at the 12 hour level and not at 42 and 72 hr may be due to the longer time intervals in the latter two time points where the plasma levels have decreased sufficiently to pose no significant differences on being challenged. This has to be confirmed by quantitation of the plasma levels.

iii. Respiratory Function

Table 10 shows the results of the analysis of respiratory rate. Only time effects showed any significance with no significant differences with the other main effects and interactions. The time factor on its own however is not important. Therefore, since there were no significant effect on respiratory rate, it can be concluded that adequate blocking activity was provided to counteract the respiratory depression activity of heroin.

iv. Pupillometry

Table 11 shows the results for pupillometry. There were significant differences with treatment and time on their own and also the interaction between time

TABLE 10

ANOVA TABLE FOR RESPIRATORY RATE

Source of Variation	SS	df	MS	F	P
A	23.567	2	11.783	1.598	NS
B	11.18	1	11.18	1.516	NS
AXB	18.04	2	9.02	1.223	NS
Error	235.931	32	7.372	-	-
C	41.808	3	13.936	4.322	0.006
AXC	18.335	6	3.055	0.947	NS
BXC	14.928	3	4.976	1.543	NS
AXBXC	29.354	6	4.892	1.517	NS
Error	309.522	96	3.224	-	-

A = Ethnicity B = Treatment C = Challenge Time

TABLE 11

ANOVA TABLE FOR PUPILLOMETRY

Source of Variation	SS	df	MS	F	P
A	0.197	2	0.098	0.107	NS
B	23.741	1	23.741	25.954	<0.001
AXB	2.512	2	1.256	1.373	NS
Error	29.27	32	0.914	-	-
C	15.852	3	5.284	22.469	<0.001
AXC	1.383	6	0.23	0.98	NS
BXC	21.454	3	7.151	30.409	<0.001
AXBXC	2.097	6	0.349	1.486	NS
Error	22.576	96	0.235	-	-

A = Ethnicity B = Treatment C = Challenge Time

and treatment. The data for the interaction were further analysed and presented in Table 12. Time effects were significant for heroin but not for placebo. Therefore, the difference in pupil response to time of challenge is significant for the heroin treated group but not for the placebo group. In the case of treatment effects, significance was observed at the 48 and 72 hours challenges. It can therefore be concluded that differences in pupil response between heroin and placebo treatment were significant at the 48 and 72 hr challenges. The naltrexone is able to block pupil response to heroin at the 12 and 24 hour challenges but not at 48 and 72 hour challenges. This could be related to the declining plasma levels of naltrexone. This can be further confirmed by quantitative analysis of the naltrexone plasma levels.

1.2 Psychological Assessment

To determine the naltrexone dosage for narcotic agonist blockade in detoxified Asian addicts, psychological assessment data using the ARCI Short Form List 116, Scales 2, 3 and 4 were obtained and analysed.

i. Methods

Each true question from Scales 2, 3 and 4 were scored as either 0 (symptom not present - false) or "1"

TABLE 12

ANOVA TABLE FOR BC INTERACTIONS

(Pupillometry)

Source of Variation	SS	df	MS	F	P
C at b_1	0.7556	3	0.2518	1.0714	NS
C at b_2	38.06	3	12.6866	53.985	$P < 0.01$
Error Term	22.576	96	0.235	-	-
B at c_1	0.0053	1	0.0053	0.0131	NS
B at c_2	1.3695	1	1.3695	3.3831	NS
B at c_3	5.94	1	5.94	14.6739	$P < 0.01$
B at c_4	39.35	1	39.35	97.2084	$P < 0.01$
Error Term	51.8144	128	0.4048	-	-

B = Treatment C = Challenge Time

(symptom present - true). The only false question (#52 of Scale 4) was converted, i.e. a true answer was scored as a "0" and a false answer was scored as a "1". For each patient, a composite score was calculated by adding up all items at each challenge time point. Thus, the highest possible score for any patient was 36. A data listing of these scores is contained in Table 13A to 13C.

The dependent variable chosen was the difference between the average of the three scores post-drug injection (5-, 30- and 60-min post-injection) and the pre-drug injection score for the 12-, 24- and 48-hr drug challenge. For the 72-hr drug challenge, the difference was between the average of the 5- and 30-min post-injection scores and the pre-injection data. The dependent variable was chosen in this manner because:

1. there was no evidence of any difference between the three post-injection scores;
2. there was a decreasing trend in the pre-injection scores. Thus, differences were calculated from each challenge pre-score rather than the initial 12-hr pre-score.

Tables 13A, 13B and 13C show the patient scores from ARCI Short Form List 116 for ethnic groups, Malay, Chinese and Indian patients respectively.

TABLE 13A: PATIENT SCORES FROM ARCI SHORT FORM LIST 116

ETHNICITY MALAY

		12 Hour		24 Hour			48 Hour			72 Hour		
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Treatment	Patient												
Placebo	N01	20	25	29	27	26	22	21	28	22	20	18	16
	N02	22	10	10	14	8	8	8	10	5	7	7	7
	N07	20	25	25	27	24	24	23	22	20	21	19	18
	N11	27	26	28	26	30	23	27	24	19	12	9	9
	N12	22	23	20	21	20	21	24	22	20	20	20	20
	N16	18	11	12	12	14	12	12	10	15	12	12	11
	N17	15	20	21	20	18	19	17	17	13	15	17	14
Heroin	Patient												
	N04	21	17	17	17	17	18	19	17	16	17	18	18
	N05	25	7	7	24	22	12	23	13	22	24	20	21
	N06	6	7	7	7	6	6	8	5	9	7	7	8
	N08	22	12	12	15	10	14	17	16	13	15	17	17
	N09	21	16	17	17	20	18	17	19	20	20	21	21
	N10	16	18	19	17	7	15	20	11	13	22	20	13
	N15	18	28	27	24	15	25	27	26	15	9	12	12

NOTE: A PATIENT'S SCORE AT EACH TIME POINT WAS DETERMINED BY THE NUMBER OF QUESTIONS ANSWERED TRUE FOLLOWING CONVERSION OF QUESTION #52. HIGHEST POSSIBLE SCORE IS 36

NA = NOT AVAILABLE

TABLE 13B: PATIENT SCORES FROM ARCI SHORT FORM LIST 116

ETHNICITY CHINESE

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Treatment	Patient																
Placebo	N18	23	16	14	13	14	13	13	12	12	11	14	14	18	18	19	NA
	N21	24	10	9	9	8	8	10	7	7	7	8	8	8	8	9	NA
	N22	25	24	20	16	17	17	17	17	17	17	17	17	17	17	17	NA
	N28	27	23	22	21	19	19	20	18	23	19	22	14	11	12	13	NA
	N29	20	18	17	17	19	13	13	14	8	11	11	9	9	10	10	NA
	N30	13	21	21	20	22	23	22	19	21	20	17	19	19	19	22	NA
	N31	23	19	12	14	14	19	10	13	18	13	14	14	12	22	16	NA
Heroin	Patient																
	N19	17	17	16	17	16	23	19	21	19	23	22	22	18	26	28	NA
	N20	23	26	24	24	22	21	21	22	22	22	22	22	24	24	29	NA
	N23	23	18	19	17	23	25	24	24	25	29	29	31	24	30	30	NA
	N24	14	10	11	8	7	9	8	6	7	8	7	7	7	11	7	NA
	N25	12	11	10	10	11	11	10	10	10	11	12	11	10	21	20	NA
	N26	7	9	8	8	7	8	8	9	7	8	8	8	7	9	8	NA
	N27	11	5	6	7	11	8	4	3	2	7	7	6	1	15	6	NA

NOTE: A PATIENT'S SCORE AT EACH TIME POINT WAS DETERMINED BY THE NUMBER OF QUESTIONS ANSWERED TRUE FOLLOWING CONVERSION OF QUESTION #52. HIGHEST POSSIBLE SCORE IS 36

NA = NOT AVAILABLE

TABLE 13C: PATIENT SCORES FROM ARCI SHORT FORM LIST 116

ETHNICITY INDIAN

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Treatment	Patient																
Placebo	N32	12	8	5	13	15	9	10	10	9	12	11	10	12	14	13	NA
	N35	35	14	14	14	13	14	14	14	10	17	17	17	14	12	12	NA
	N36	15	16	17	12	14	12	11	11	13	9	8	8	9	9	7	NA
	N39	6	5	6	6	7	5	5	5	7	5	5	5	12	8	8	NA
	N41	14	12	8	11	10	6	4	7	3	5	6	4	5	5	8	NA
Heroin	Patient																
	N33	8	6	6	10	8	8	7	6	9	8	11	8	9	16	10	NA
	N34	21	28	29	28	28	18	20	22	17	17	14	15	8	17	15	NA
	N37	27	21	18	23	21	25	21	20	23	18	17	15	14	11	12	NA
	N38	12	19	22	20	12	24	22	22	10	25	25	24	1	29	25	NA
	N40	18	21	16	11	22	19	22	22	15	23	26	26	15	27	25	NA

NOTE: A PATIENT'S SCORE AT EACH TIME POINT WAS DETERMINED BY THE NUMBER OF QUESTIONS ANSWERED TRUE FOLLOWING CONVERSION OF QUESTION #52. HIGHEST POSSIBLE SCORE IS 36

NA = NOT AVAILABLE

A summary table of the mean scores at each challenge timepoint is contained in Table 14.

The experimental design which was used to analyse these differences was a split-plot three factorial design with repeated measures in one factor (Winer, 1971). The main effects of ethnicity (Malay, Chinese or Indian) and treatment (placebo or heroin) and the interaction between these factors comprised the whole plot, while the main effect of challenge time and two-factor interaction terms involving ethnicity and challenge time and treatment and challenge time, and the three-way interaction term of ethnicity, treatment and challenge time comprised the subplot. The level of significance for tests of differences in main effects was set at p = 0.05. Since the ethnicity x treatment and treatment x challenge time interactions were of particular interest, the level of significance for these interaction terms was set at relatively high levels (p = 0.20). Where any significant interaction was observed, the data were further analysed to assess the differences in each factor at various levels of the other factor.

TABLE 14: MEAN SCORES FROM ARCI SHORT FORM LIST 116

		TIME OF CHALLENGE															
		12 Hour				24 Hour				48 Hour				72 Hour			
		Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"	Pre	5"	30"	60"
Ethnicity	Treatment																
Malay	Placebo	20.1	19.0	20.3	20.3	19.3	18.0	17.9	18.6	15.9	14.9	13.9	13.4	16.3	17.0	15.9	NA
	Heroin	18.0	14.6	15.0	16.9	13.4	15.0	14.7	16.4	14.7	15.3	15.7	15.0	15.0	19.4	18.6	NA
Chinese	Treatment																
	Placebo	22.3	18.3	16.3	15.0	15.7	15.3	14.3	13.6	14.4	13.6	14.0	13.0	13.0	14.1	14.7	NA
	Heroin	14.9	13.3	12.7	12.3	13.1	14.3	12.7	12.9	12.4	14.7	14.3	14.6	12.3	18.7	17.6	NA
Indian	Treatment																
	Placebo	15.8	10.8	9.4	10.2	10.8	8.2	8.2	8.8	7.8	8.6	8.4	7.8	9.4	9.0	9.0	NA
	Heroin	17.0	18.4	17.6	17.8	18.0	18.6	17.4	17.8	13.8	17.6	18.4	17.0	9.2	19.4	17.2	NA

NA = NOT AVAILABLE

ii. Results

Table 15 provides a summary of the mean scores (pre, post and change) for each ethnic treatment group at each of the four challenge times. Table 16 contains the output of the analysis of variance results (SAS, 1985).

Overall, there was a significant treatment effect ($p = 0.0056$) and a significant time effect. When the results were pooled, there was a mean decrease of 1.3 in the scores observed (16.0 pre to 14.7 post) for the placebo group and a mean increase of 1.9 in scores (14.9 pre to 16.8 post) in the heroin-treated group.

The interaction between treatment and time were further analysed to determine whether the treatment differences were more prevalent at later challenge time points (48 and 72 hr) than at earlier times (12 and 24 hr). It was found that treatment differences occurred mainly at the later challenge time points (48 and 72 hr) indicating that narcotic blocking activity by naltrexone was effective up to 48 hr. This however needs to be correlated with plasma naltrexone levels to determine whether there are decreased levels of naltrexone accounting for the lowered narcotic blocking activity.

TABLE 15: MEAN SCORES FROM ARC1 SHORT FORM LIST 116
WITH POST SCORES (5, 30, 60) FOR EACH SUBJECT AVERAGED

	TIME OF CHALLENGE												POOLED OVER CHALLENGE TIMES		
	12 hr			24 hr			48 hr			72 hr					
	PRE	POST	CHANGE	PRE	POST	CHANGE	PRE	POST	CHANGE	PRE	POST	CHANGE	PRE	POST	CHANGE
ETHNICITY TREATMENT															
MALAY PLACEBO(N=7)	20.6	20.6	-0.0	20.0	18.8	-1.2	16.3	14.5	-1.8	16.7	16.9	0.1	18.4	17.7	-0.7
HEROIN(N=7)	18.4	15.8	-2.6	13.9	15.8	2.0	15.4	16.1	0.7	16.0	20.0	4.0	15.9	16.9	1.0
CHINESE TREATMENT															
PLACEBO(N=7)	22.1	17.0	-5.2	16.1	15.1	-1.0	15.1	14.1	-1.0	13.4	15.1	1.7	16.7	15.3	-1.4
HEROIN(N=7)	15.3	13.4	-1.9	13.9	14.0	0.1	13.1	15.3	2.2	13.0	18.9	5.7	13.8	15.4	1.6
INDIAN TREATMENT															
PLACEBO(N=5)	16.4	10.7	-5.7	11.8	9.1	-2.7	8.4	9.3	0.9	10.4	9.6	-0.8	17.2	17.3	0.1
HEROIN(N=5)	17.2	18.5	1.3	18.2	18.5	0.3	14.8	18.1	3.3	9.4	18.7	9.3	14.9	18.5	3.6
ETHNICITY POOLED OVER TREATMENTS															
MALAY(N=14)	19.5	18.2	-1.3	16.9	17.3	0.4	15.9	15.3	-0.5	16.4	18.4	2.1	17.2	17.3	0.1
CHINESE(N=14)	18.7	15.2	-3.5	15.0	14.5	-0.5	14.1	14.7	0.6	13.2	17.0	3.8	15.3	15.4	0.1
INDIAN(N=10)	16.8	14.6	-2.2	15.0	13.8	-1.2	11.6	13.7	2.1	9.9	14.7	4.3	13.3	14.1	0.8
TREATMENT POOLED OVER ETHNICITY															
PLACEBO(N=19)	20.1	16.6	-3.4	16.4	14.9	-1.5	13.8	13.0	-0.8	13.8	14.3	0.5	16.0	14.7	-1.3
HEROIN(N=19)	16.9	15.6	-1.3	15.0	15.9	0.9	14.4	16.4	1.9	13.2	19.2	6.1	14.9	16.8	1.9
POOLED OVER ETHNICITY AND TREATMENT (N=38)	18.5	16.1	-2.4	15.7	15.4	-0.3	14.1	14.7	0.6	13.5	16.8	3.3	15.5	15.7	0.3

TABLE 16: SUMMARY OF ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116
REFERENCE: WINER, B.J., STATISTICAL PRINCIPLES IN EXPERIMENTAL DESIGN, 2ND. ED., pp 559 - 571

GENERAL LINEAR MODELS PROCEDURE

DEPENDENT VARIABLE: DIFF

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	55	3012.88072786	54.77964960	2.76	0.0001	0.612610	1568.6722
ERROR	96	1905.22142857	19.84605655		ROOT MSE		DIFF MEAN
CORRECTED TOTAL	151	4918.10215643			4.45489131		0.28399123

SOURCE	DF	TYPE I SS	F VALUE	PF > F	DF	TYPE III SS	F VALUE	PR > F
A	2	12.08102548	0.30	0.7383	2	12.08102548	0.30	0.7383
B	1	393.29111842	19.82	0.0001	1	435.71147480	21.95	0.0001
A*B	2	90.30441729	2.28	0.1083	2	90.30441729	2.28	0.1083
S(A*B)	32	1576.76587302	2.48	0.0004	32	1576.76587302	2.48	0.0004
C	3	623.64820906	10.47	0.0001	3	632.88227708	10.63	0.0001
A*C	6	111.63363617	0.94	0.4720	6	111.63363617	0.94	0.4720
B*C	3	74.46984649	1.25	0.2957	3	82.94829015	1.39	0.2496
A*B*C	6	130.68660192	1.10	0.3696	6	130.68660192	1.10	0.3696

TESTS OF HYPOTHESES USING THE TYPE III MS FOR S(A*B) AS AN ERROR TERM

SOURCE	DF	TYPE III SS	F VALUE	PR > F
A	2	12.08102548	0.12	0.8850

TESTS OF HYPOTHESES USING THE TYPE III MS FOR S(A*B) AS AN ERROR TERM

SOURCE	DF	TYPE III SS	F VALUE	PR > F
B	1	435.71147480	8.84	0.0056

TESTS OF HYPOTHESES USING THE TYPE III MS FOR S(A*B) AS AN ERROR TERM

SOURCE	DF	TYPE III SS	F VALUE	PR > F
A*B	2	90.30441729	0.92	0.4102

KEY: A = ETHNICITY B = TREATMENT C = CHALLENGE TIME S(A*B) = SUBJ W. groups (error (between))

The analysis of the interaction between treatment and challenge time is contained in Table 17 and is also graphically illustrated in Figure 2. Mean scores can be found in the second and third rows from the bottom of Table 15.

From this analysis , the following were noted:

1. The mean change in score (post-pre) was increasing in both treatment groups.

2. The magnitude of the mean difference between the placebo and heroin groups remained relatively constant at 12, 24 and 48 hr (-3.4 - (-1.3) = 2.1, 2.4, 2.7, respectively), but increased substantially at 72 hr (5.6).

3. Statistical analysis was carried out at each time of challenge. It was found that statistical significance was only obtained at 72 hr time of challenge ($p < 0.001$).

TABLE 17

ANOVA TABLE FOR BC INTERACTIONS
(Mean change from pre-injection score for overall response to ARCI short form list 116)

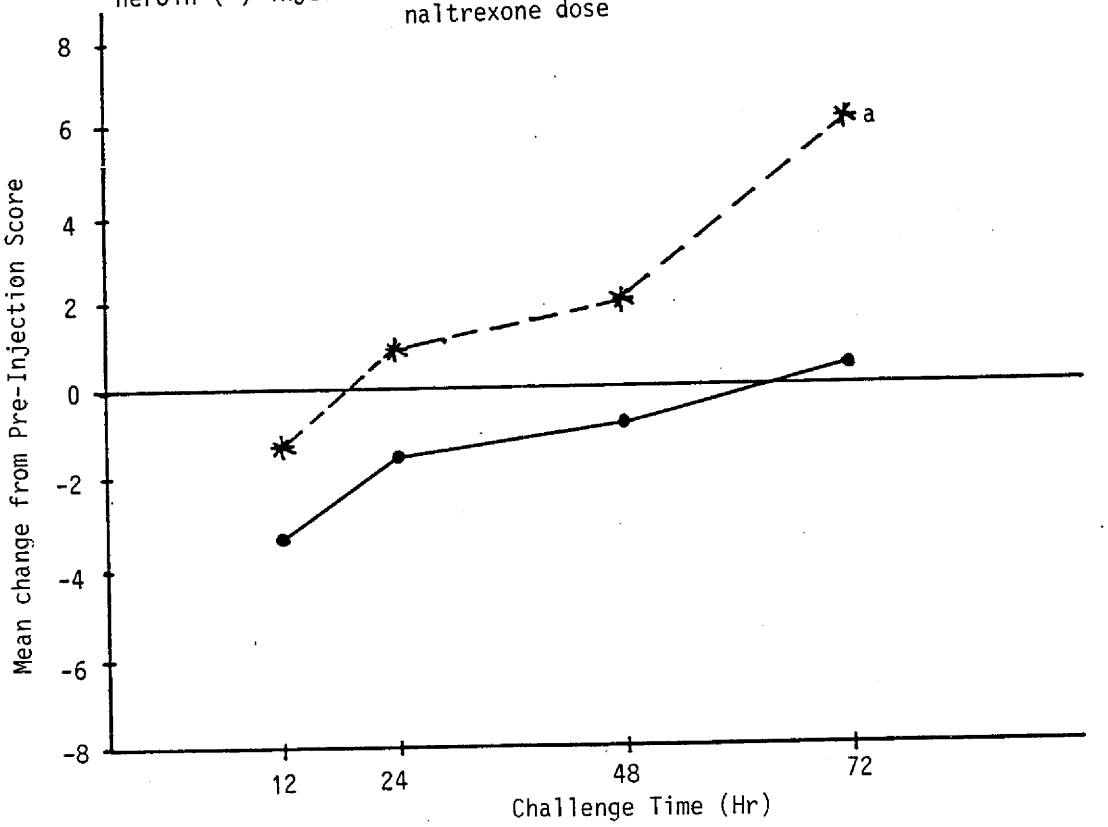
Source of Variation	SS	df	MS	F	P-Value
C at b_1	149.2222	3	49.7407	2.506	.064
C at b_2	548.8958	3	182.9653	9.219	<.001
Error	1905.2214	96	19.8461		
B at C_1	41.4064	1	41.4064	1.522	.220
B at C_2	54.8801	1	54.8801	2.017	.158
B at C_3	74.9942	1	72.9942	2.683	.104
B at C_4	298.4802	1	298.4802	10.972	.001
Error	3481.9873	128	27.2030		

B = Treatment

C = Challenge Time

FIGURE 2

Mean change from pre-injection score for overall response to ARCI short-form in subjects receiving placebo (●) or heroin (*) injections 12, 24, 48 and 72 hrs after last naltrexone dose



"a" refers to statistically significantly difference from placebo group

TABLE 18

MULTIVARIATE ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116

GENERAL LINEAR MODELS PROCEDURE

REPEATED MEASURES ANALYSIS OF VARIANCE

REPEATED MEASURES LEVEL INFORMATION

DEPENDENT VARIABLE HR12_DIF HR24_DIF HR48_DIF HR72_DIF

LEVEL OF TIME 12 24 48 72

MANOVA TEST CRITERIA AND EXACT F STATISTICS FOR THE HYPOTHESIS OR NO TIME EFFECT

H = TYPE III SS&CP MATRIX FOR: TIME E = ERROR SS&CP MATRIX

S=1 M=0.5 N=14.5

STATISTIC	VALUE	F	NUM DF	DEN DF	PR > F
WILKS' LAMBDA	0.4465621	12.39	3	30	0.0001
PILLAI'S TRACE	0.5534379	12.39	3	30	0.0001
HOTELLING-LAWLEY TRACE	1.23933	12.39	3	30	0.0001
ROY'S GREATEST ROOT	1.23933	12.39	3	30	0.0001

MANOVA TEST CRITERIA AND F APPROXIMATIONS FOR THE HYPOTHESIS OF NO TIME*ETHNIC EFFECT

H = TYPE III SS&CP MATRIX FOR: TIME*ETHNIC E = ERROR SS&CP MATRIX

S=2 M=0 N=14.5

STATISTIC	VALUE	F	NUM DF	DEN DF	PR > F
WILKS' LAMBDA	0.820244	1.04	6	60	0.4078
PILLAI'S TRACE	0.1853214	1.05	6	62	0.3990
HOTELLING-LAWLEY TRACE	0.2123645	1.02	6	58	0.4175
ROY'S GREATEST ROOT	0.1731875	1.79	3	31	0.1697

NOTE: F STATISTIC FOR ROY'S GREATEST ROOT IS AN UPPER BOUND

F STATISTIC FOR WILKS' LAMBDA IS EXACT

REFERENCE: COLE, I.W. AND GRIZZLE, I.E. (1966), "APPLICATIONS OF MULTIVARIATE ANALYSIS OF VARIANCE TO REPEATED MEASURES EXPERIMENTS" BIOMETRICS, 22, 810 - 828

TABLE 18

MULTIVARIATE ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116

MANOVA TEST CRITERIA AND EXACT F STATISTICS FOR THE HYPOTHESIS OR NO*TRT TIME EFFECT

H = TYPE III SS&CP MATRIX FOR: TIME*TRT E = ERROR SS&CP MATRIX

S=1 M=0.5 N=14.5

STATISTIC	VALUE	F	NUM DF	DEN DF	PR > F
WILKS' LAMBDA	0.80995	2.346	3	30	0.0926
PILLAI'S TRACE	0.19005	2.346	3	30	0.0926
HOTELLING-LAWLEY TRACE	0.234644	2.346	3	30	0.0926
ROY'S GREATEST ROOT	0.234644	2.346	3	30	0.0926

MANOVA TEST CRITERIA AND F APPROXIMATIONS FOR THE HYPOTHESIS OF NO TIME*ETHNIC*TRT EFFECT

H = TYPE III SS&CP MATRIX FOR: TIME*ETHNIC*TRT E = ERROR SS&CP MATRIX

S=2 M=0 N=14.5

STATISTIC	VALUE	F	NUM DF	DEN DF	PR > F
WILKS' LAMBDA	0.8194136	1.047	6	60	0.4044
PILLAI'S TRACE	0.1887836	1.077	6	62	0.3860
HOTELLING-LAWLEY TRACE	0.2103811	1.017	6	58	0.4235
ROY'S GREATEST ROOT	0.1377676	1.424	3	31	0.2546

NOTE: F STATISTIC FOR ROY'S GREATEST ROOT IS AN UPPER BOUND

F STATISTIC FOR WILKS' LAMBDA IS EXACT

REFERENCE: COLE, I.W. AND GRIZZLE, I.E. (1966), "APPLICATIONS OF MULTIVARIATE ANALYSIS OF VARIANCE TO REPEATED MEASURES EXPEIRMENTS" BIOMETRICS, 22, 810 - 828

TABLE 18

MULTIVARIATE ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116

GENERAL LINEAR MODELS PROCEDURE

TESTS OF HYPOTHESES FOR BETWEEN SUBJECTS EFFECTS

SOURCE	DF	TYPE III SS	MEAN SQUARE	F VALUE	PR > F
ETHNIC	2	12.08102548	6.04051274	0.12	0.8850
TRT	1	440.58544001	440.58544001	8.94	0.0053
ETHNIC*TRT	2	90.30441729	45.15220865	0.92	0.4102
ERROR	32	1576.76587302	49.27393353		

REFERENCE: COLE, I.W. AND GRIZZLE, I.E. (1966). "APPLICATIONS OF MULTIVARIATE ANALYSIS OF VARIANCE TO REPEATED MEASURES EXPERIMENTS", BIOMETRICS, 22, 810 - 828

TABLE 18

MULTIVATE ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116

ANALYSIS OF VARIANCE OF CONTRAST VARIABLES

TIME N REPRESENTS THE NTH DEGREE POLYNOMIAL CONTRAST FOR TIME

CONTRAST VARIABLE: TIME 1

SOURCE	DF	TYPE III SS	MEAN SQUARE	F VALUE	PR > F
MEAN	1	610.60885211	610.60885211	27.17	0.0001
ETHNIC	2	81.91317117	40.95658558	1.82	0.1780
TRT	1	60.61280692	60.61280692	2.70	0.1103
ETHNIC*TRT	2	10.65282822	5.32641411	0.24	0.7904
ERROR	32	719.21077482	22.47533671		

CONTRAST VARIABLE: TIME 2

SOURCE	DF	TYPE III SS	MEAN SQUARE	F VALUE	PR > F
MEAN	1	0.05177604	0.05177604	0.00	0.9641
ETHNIC	2	5.99438840	2.99719420	0.12	0.8879
TRT	1	21.15151431	21.15151431	0.84	0.3656
ETHNIC*TRT	2	87.73264934	43.86632467	1.75	0.1905
ERROR	32	803.44807100	25.10775222		

CONTRAST VARIABLE: TIME 3

SOURCE	DF	TYPE III SS	MEAN SQUARE	F VALUE	PR > F
MEAN	1	22.22164892	22.22164892	1.86	0.1823
ETHNIC	2	23.72607660	11.86303830	0.99	0.3818
TRT	1	1.18396892	1.18396892	0.10	0.7550
ETHNIC*TRT	2	32.30112436	16.15056218	1.35	0.2734
ERROR	32	382.56258276	11.95508071		

REFERENCE: COLE, I.W. AND GRIZZLE, I.E. (1966). "APPLICATIONS OF MULTIVARIATE ANALYSIS OF VARIANCE TO REPEATED MEASURES EXPERIMENTS" BIOMETRICS. 22, 810-828

TABLE 18

MULTIVARIATE ANALYSIS OF VARIANCE OF SUBJECT SCORES FROM ARCI SHORT FORM LIST 116

GENERAL LINEAR MODELS PROCEDURE

UNIVARIATE TESTS OF HYPOTHESES FOR WITHIN SUBJECT EFFECTS

SOURCE	DF	TYPE III SS	MEAN SQUARE				
TIME	3	632.88227708	210.96075903	10.63	0.0001	0.0001	0.0001
TIME*ETHNIC	6	111.63363617	18.60560603	0.94	0.4720	0.4503	0.4630
TIME*TRT	3	82.94829015	27.64943005	1.39	0.2496	0.2555	0.2530
TIME*ETHNIC*TRT	6	130,68660192	21.78110032	1.10	0.3696	0.3661	0.3686
ERROR (TIME)	96	1905.22142857	19.84605655	1.10	0.3696	0.3661	0.3686

GREENHOUSE-GEISSER EPSILON = 0.6920

HUYNH-FELOT EPSILON = 0.8565

REFERENCE: COLE, I.W. AND GRIZZLE, I.E. (1966), "APPLICATIONS OF MULTIVARIATE ANALYSIS OF VARIANCE TO REPEATED MEASURES EXPERIMENTS", BIOMETRICS, 22, 810-828

FIGURE 3

Mean Change from Pre-Injection Score (ARCI Short Form Scales 2, 3 & 4) at each Challenge Time by Treatment Group

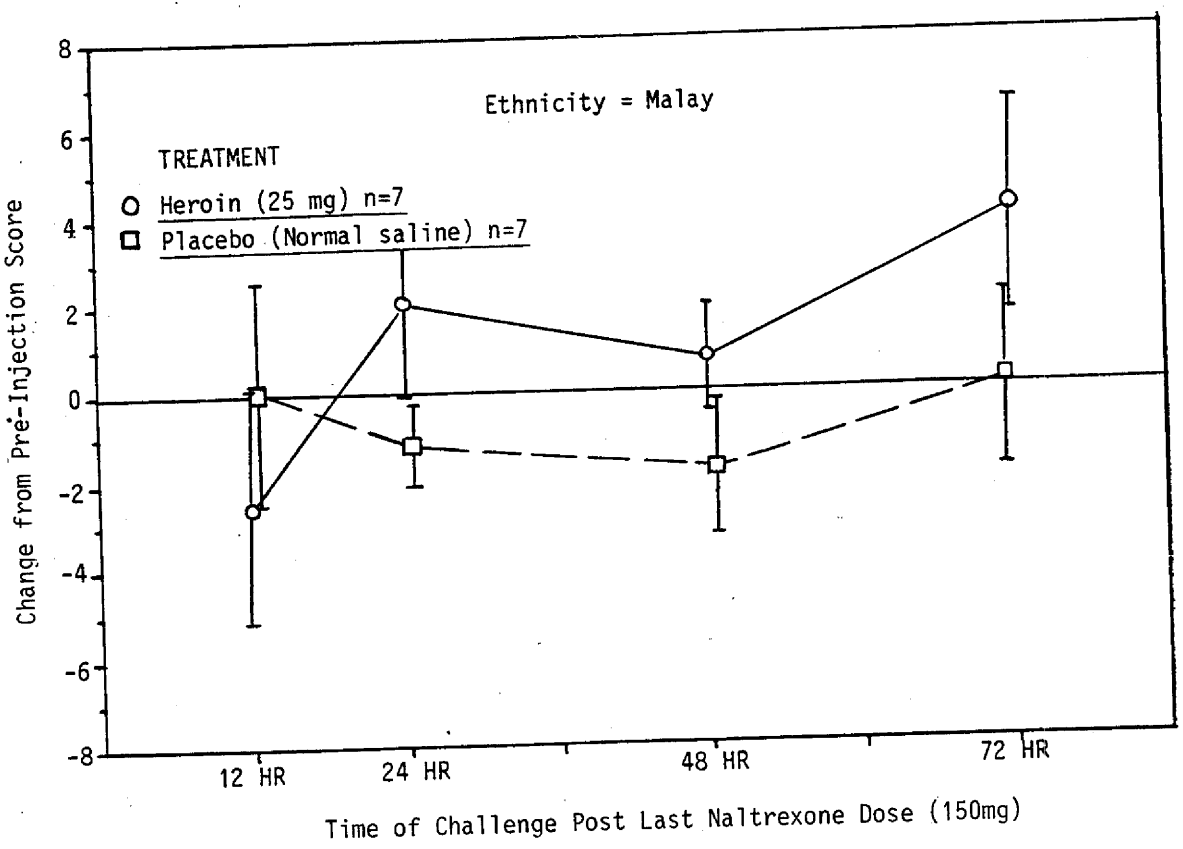


FIGURE 4

Mean Change from Pre-Injection Score (ARCI Short Form Scales 2, 3, & 4) at each Challenge Time by Treatment Group

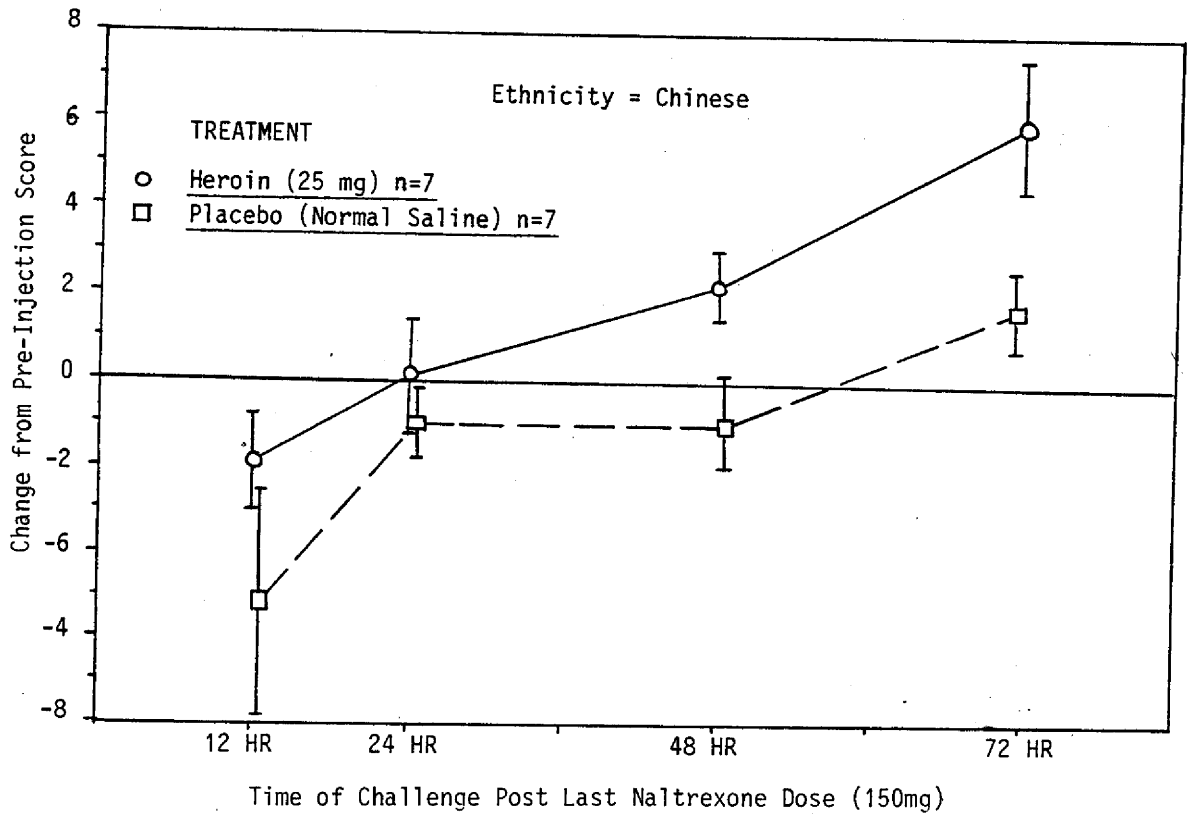
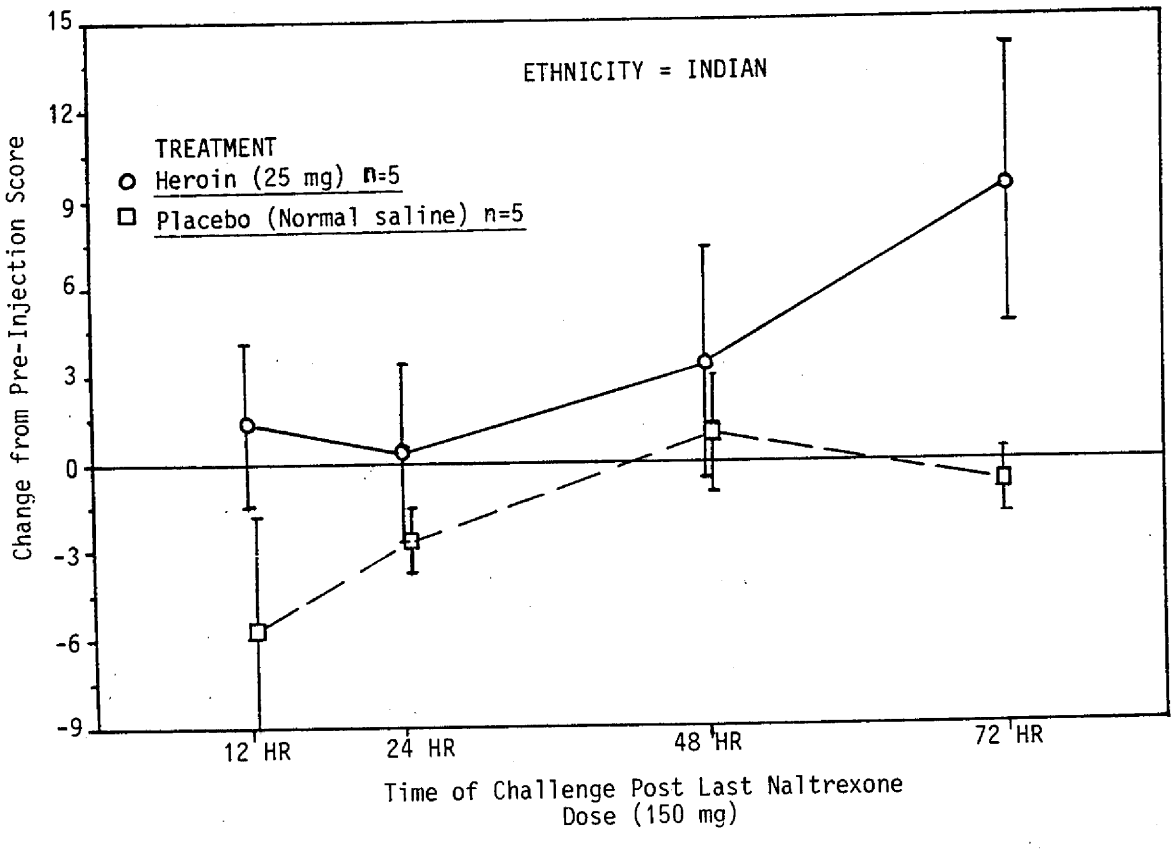


FIGURE 5

Mean Change from Pre-Injection Score (ARCI Short Form Scales 2, 3 & 4) at each Challenge Time, by Treatment Group



Supporting evidence of the interaction between treatment and challenge time is contained in Table 18 which provides the output of a multivariate analysis as given in Cole and Grizzle (1966). The p-value for the treatment-by-time interaction for this analysis was 0.093.

For both analyses, there was no evidence of ethnic differences nor any significant interactions involving this factor. For illustrative purposes, the mean changes over time for each ethnic group are plotted in Figures 3-5.

1.3 FOLLOW-UP ON POST-TRIAL PSYCHOLOGICAL SYMPTOMS

Following the trial there was a 4 day follow-up of all the subjects. They were assessed for craving for drug and withdrawal symptoms. The withdrawal symptoms that were charted twice a day were yawning, perspiration, running nose, lacrimation, mydriasis, goose flesh, tremors, hot and cold flushes, aching bones and muscles, anorexia, restlessness, nausea, vomiting and diarrhoea. Blood pressure, temperature, pulse and respiratory rates were also monitored twice a day. The results are

summarised in Table 19. In the table, a '+' sign indicates that the subject had a number of symptoms to suggest withdrawal. Where there were some symptoms and others absent and it was not conclusive enough to suggest withdrawal ± was used. N_1 had both craving throughout the 4 days and withdrawal symptoms on the first day though he had only placebo. In fact, Table 19 shows both craving as well as withdrawal symptoms to be more in the placebo group. Hence, it can be concluded that clinically there was no significant difference in the post trial period in between the two groups.

1.4 QUANTITATIVE ANALYSIS OF PLASMA SAMPLES

Plasma samples were taken from 31 subjects (irregardless of race) following the third naltrexone dose at times, 0, 1/2, 6, 9, 12, 24, 48 and 72 hours after the dose. The results are presented in Table 20 and Figures 6 and 7. The plasma concentrations of both naltrexone and naltrexol were rather variable among the subjects studied with coefficients of variation ranging from 96-324% for naltrexone and 49-268% for naltrexol.

Table 19

4 day Follow-Up on Post-Trial Symptoms

	PLACEBO				HEROIN	
	Craving	Withdrawal Symptoms		Pupillary sign after (Hrs)	Craving	Withdrawal Symptoms
Malays			Malays			
N1	+	+	N4	48	-	-
N2	-	-	N5	72	-	-
N7	-	+	N6	72	-	-
N11	-	-	N8	72	-	-
N12	-	+	N9	72	-	+
N16	-	-	N10	-	-	-
N17	-	+	N15	24	-	-
Chinese			Chinese			
N18	-	-	N19	24	-	-
N21	-	-	N20	24	-	-
N22	-	-	N23	72	-	-
N28	+	+	N24	72	-	-
N29	-	-	N25	72	-	-
N30	+	+	N26	24	-	-
N31	-	-	N27	72	-	-
Indian			Indian			
N32	-	-	N33	72	-	-
N35	-	-	N34	48	-	-
N36	-	-	N37	72	-	+
N39	-	+	N38	24	-	+
N41	-	-	N40	72	-	+

TABLE 20

Mean Plasma Concentrations (ng/ml) of Naltrexone and Naltrexol

Time (Hour)	No. Subjects	Naltrexone	Naltrexol
0	25	6.57	16.18
0.5	25	29.50	173.30
6.0	31	11.70	128.97
9.0	29	4.05	88.68
12.0	17	1.92	52.98
24.0	30	0.31	25.61
48.0	30	0.06	9.31
72.0	31	0.00	3.42

FIGURE 6: The Mean Plasma Concentration with Time of Naltrexone following the Third Naltrexone Dose in All Subjects Irregardless of Ethnic Group

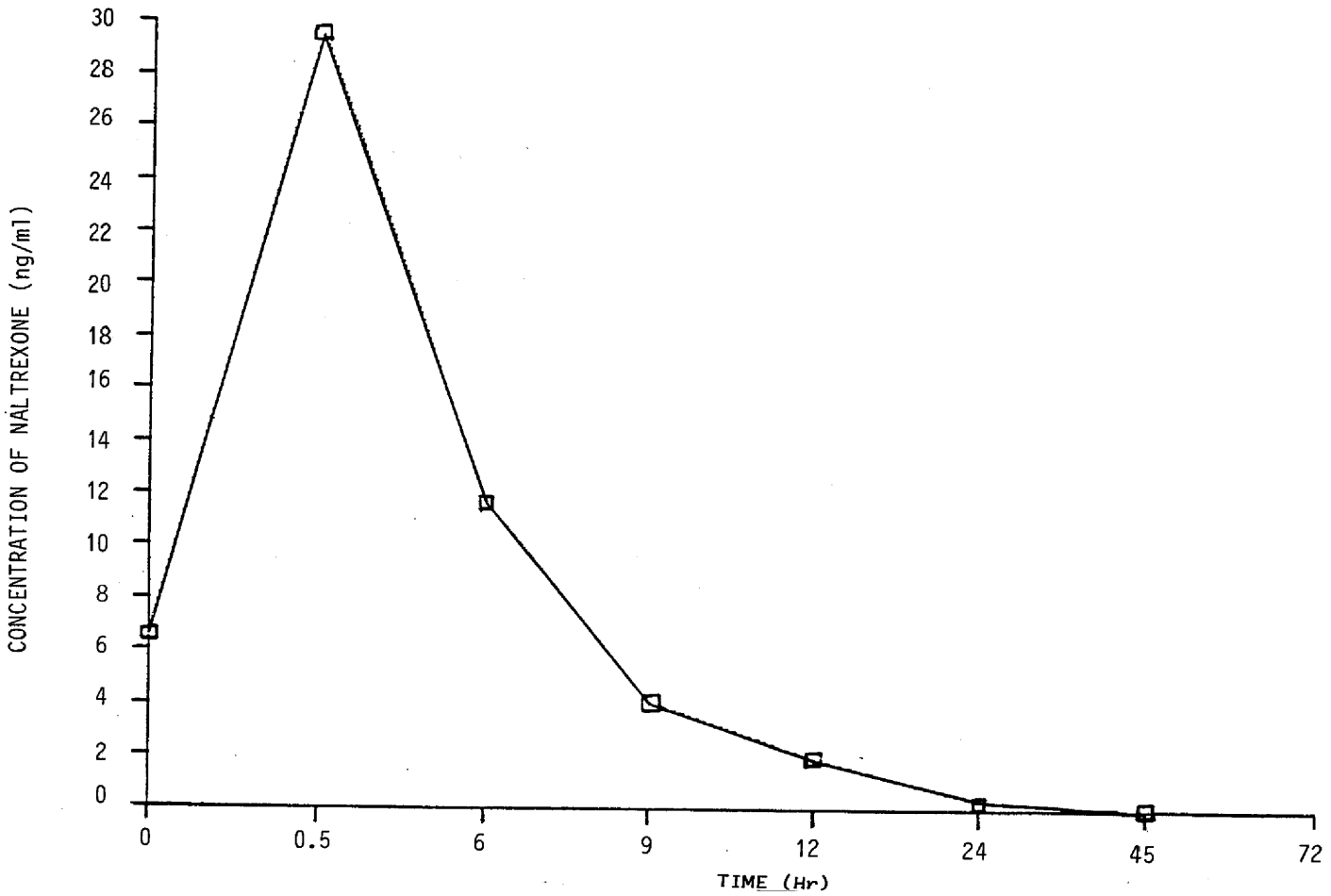
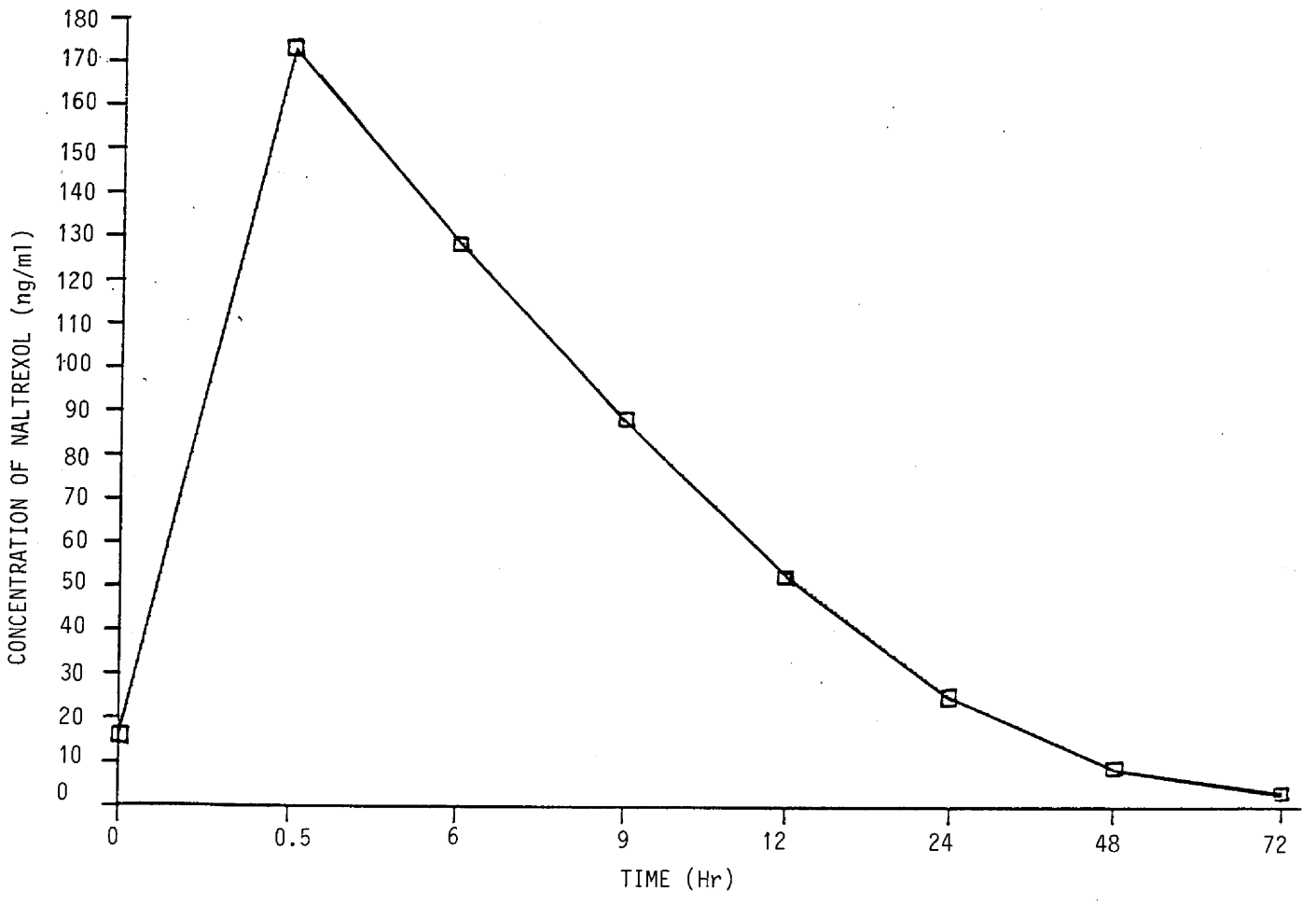


FIGURE 7: The Mean Plasma Concentration with Time of Naltrexol following the Third Naltrexone Dose in All Subjects Irregardless of Ethnic Group



2. DISCUSSION

Both the naltrexol and naltrexone peaked around half an hour after drug administration with the naltrexone showing a faster rate of elimination than the naltrexol. Since naltrexone is more active than naltrexol (Blumberg and Ikeda, 1976) the naltrexone concentration-time profile is important. The naltrexone levels at 48 hrs was 0.06 ± 0.43 ng/ml and was not detectable at 72 hours. At these latter times there were significant differences in pupil response between heroin and placebo treatment. This observation was attributed to low plasma levels and the quantitative data confirms this observation. This view is supported by Verebey (1981) who found that the lowest effective naltrexone plasma level was 2.00 ng/ml which provided an average of 86.5 % blockade of the effects of 25 mg heroin.

No information on the activity of naltrexol has been found in man though Blumberg and Ikeda (1976) have done some work with rats and mice. They found that naltrexol compared to naltrexone was 1/56 as active in rats and 1/2 as active in mice in preventing the loss of righting reflex from morphine sulfate. Also with the use of equi-antagonist doses of naltrexone and naltrexol, they found that naltrexol was four and nine times as long-acting as naltrexone in rats and mice respectively. Blumberg and Ikeda therefore suggested that their

findings of prolonged activity of naltrexol may support the view that naltrexol contributes to the comparatively long narcotic blockade observed after oral naltrexone administration in man.

Verebey (1981) found that with 100 mg/day naltrexone therapy and 25 mg heroin challenges at 24, 48 and 72 hr after the last naltrexone dose that narcotic blockade for the psychological responses seem to last longer and to a greater extent than physiological responses of pupillary miosis and respiratory depression. He found that blockade for pooled pupillary miosis and respiratory depression was 89% at 24 hr, 73 % at 48 hr and 20% at 72 hr after the last naltrexone dose. For blockade of physiological responses,it was 99% at 24 hr, 92% at 48 hr and 57% at 72 hr after the last naltrexone dose.

Our study differed from Verebey in that not only was pupillary miosis and respiratory depression data obtained but other physiological responses like systolic blood pressure and heart rate were also monitored. Our results show that naltrexone adequately blocked the opiate effects on all the above physiological responses except for pupillary miosis. Naltrexone is able to block pupil response to heroin at the 12 and 24 hr challenges but not at the 48 and 72 hr challenges. Verebey however still found narcotic blockade of pupil response at 48 hr (73%).

CHAPTER IV

1. CONCLUSION

1.1 Physiological Data

Since for safety reasons, respiratory and cardiovascular parameters are of major concern, there appeared to be adequate blockade of these parameters at 72 hours. Treatment differences between heroin and placebo were seen when pupil response was measured at the 48 and 72 hr challenge. This suggested that the naltrexone levels may have decreased to a level at 48 hr, that is not adequate to block the narcotic effect of heroin on pupil response. This was confirmed by plasma levels of naltrexone. Therefore for adequate blockade of the narcotic effect of heroin on pupil response, naltrexone levels must be above 0.06 ng/ml. However pupil response blockade is not a major finding where efficiency is concerned.

Post-trial follow-up assessments craving and withdrawal symptoms showed no significant differences between placebo or heroin-treated groups.

1.2 Psychological Data

Psychological assessment data showed that naltrexone was able to provide narcotic blockade for as long as 48 hr. This result correlates with the physiological data i.e. pupil response. Plasma naltrexone levels were not present at 72 hr indicating a reason for no narcotic blockade.

Also, with both physiological and psychological assessments, there were no significant response differences between the three ethnic groups studied. Naltrexone treatment showed similar responses upon narcotic challenge in all three ethnic groups.

The study has shown that the recommended dosage regimen of 100 mg for 48 hours provide adequate blockade for the said period. However the dosage of 150 mg for 72 hours was found to allow limited heroin effects for the last 12-14 hours of this period. Hence, for the Malaysian population where heroin tolerance is relatively high, it is suggested that consideration be given to a regimen of 100 mg every 2 days and for 3 day periods a 200 mg dose be prescribed. However, this will be at the discretion of the Physician and will also depend on the drug history of the subject.

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