

Comparative Study Of Verapamil And Amitriptyline In Acute Opioid Abstinence Syndrome

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ABSTRACT:

Objective: To evaluate the effectiveness of verapamil and amitriptyline in the treatment of acute opioid withdrawal syndrome in patients with chronic dependence on opioids.

Materials and Methods: The study was conducted at Psychological Medicine Ward, Civil Hospital Karachi and Arshi Hospital, Naseerabad, F.B.area, Karachi. A total of forty (40) patients were admitted for ten (10) days in hospital. No treatment was given during the first two days of admission after abrupt termination of opioid to observe the acute opioid withdrawal signs and symptoms. Patients were divided into 2 groups. Each group had 20 opiate addicts. One group was given verapamil orally in a 40mg dose thrice daily and the other group was given amitriptyline orally in a 10mg dose thrice daily from day 3 to day 9 of admission. The intensity of signs and symptoms were recorded by using subjective and objective opiate withdrawal questionnaire. Urine analysis for opioids was done on day 1, 5 and 10 of admission.

Results: Verapamil in comparison to amitriptyline significantly decreased the intensity of signs and symptoms of acute opioid withdrawal from day 4 to day 10 of admission. Urine analyses for opioids were positive on day 01 while zero on day 10.

Conclusion: Verapamil in comparison to amitriptyline was found to be safe and effective for the treatment of signs and symptoms of acute opioid withdrawal in in-door patients without any significant side effects.

Keywords: Opioids, In-patients Verapamil, Amitriptyline, Acute abstinence syndrome.

INTRODUCTION:

The term opioid is used to designate a group of drugs that are, to varying degrees, opium or morphine like in their properties.¹ The word opium is derived from OPOS, the Greek word for juice, the drug being derived from the juice of the opium poppy, *Papaver somniferum*.² Opioid drugs are used primarily for the treatment of pain. Some of the CNS mechanisms that reduce the perception also produce a state of well-being or euphoria. Thus, opioid drugs also are taken outside of medical channels for the purpose of obtaining the effects on mood. One of the hazards in the use of opioids to alter mood and feeling is that some individuals eventually develop drug abuse and drug addiction.³ The most commonly abused drugs in this group are heroin, morphine, oxycodone and meperidine.⁴

Opioid abstinence syndrome has been a medical problem

ever since the availability of opioid drugs. In addition with powerful withdrawal symptoms during abstinence, opioid relapses were difficult to prevent without an adequate treatment program. Successful approaches to pharmacotherapy in opioid addiction continue to rely largely on substitution of short-acting agonists such as heroin and oral administration of long acting high-efficacy agonists (methadone) or partial agonists (buprenorphine).^{5,6} Notably, all opioids that produce analgesia also can cause tolerance, addiction and withdrawal and all of the available opioids are misused.⁷ Hence it necessitates the search for a non-opioid treatment for opioid detoxification and dependence.^{8,9,10}

Amitriptyline, an antidepressant drug is now a days widely used for controlling opioid abstinence. However evidence of its efficiency in the management of withdrawal from opioids is scanty.¹¹ On the other hand Calcium (Ca⁺⁺) channel blocking drugs are reported to decrease the severity of opioid withdrawal in rats.^{11,12} Calcium channel blockers also reduced the body weight loss and diarrhea of abstinence as produced by naloxone in morphine dependent animals.^{13,14} With this background present study was designed to evaluate the effectiveness of a calcium (Ca⁺⁺) channel blocking drug, verapamil and an antidepressant drug amitriptyline in the treatment of acute opioid withdrawal syndrome in patients with chronic dependence on opioids.

MATERIALS AND METHODS:

This study was carried out in the department of Pharmacology and Therapeutics Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre (JPMC), Karachi. The forty selected opioid addicts between 21 and 45 years of age seeking treatment for opioid dependence of at least 4 months of duration were enrolled and admitted to the inpatient Psychological Medicine ward, Civil Hospital Karachi and Arshi Hospital Naseerabad F.B area Karachi for ten days. Patients having any psychiatric illness, systemic or debilitating disease or dependence on other drug in addition to opioids were excluded.^{15,16} The materials used were tablet verapamil (calan, calcium channel blocker orally in a dose of 40mg thrice daily), tablet amitriptyline (tryptanol, an antidepressant orally in a dose of 10mg thrice daily) and the Front line

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Opiates Test Strips.

Parameters: The patients were assessed on the basis of following parameters:

(1) Subject – Reported Measures: They were in the form of subjective opiate withdrawal scale (SOWS) which contained twenty one typical opiate withdrawal symptoms (muscle cramps, flushing, painful joints, yawning, restlessness, watery eyes, runny nose, chill or gooseflesh, sick to stomach, sneezing, abdominal cramps, irritability, backache, tense and jittery, sweating, depressed, trouble getting to sleep, shaky or tremulous, hot or cold flashes, bothered with noise, and skin clammy and damp).¹⁵

(2) Observer – Rated Measures: They were in the form of objective opiate withdrawal scale (OOWS) containing six observable physical signs (lacrimation, rhinorrhea, yawning, perspiration, piloerection or gooseflesh and restlessness). The intensity of signs and symptoms were rated on a five point graded scale in which 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely.¹⁵

(3) Urinalysis Measures: Urine samples were collected on day 1, 5 and 10 of admission. All samples were collected under staff observation to deter bogus urine samples and tested immediately for opioids by using one-step dip and-read chromatographic test strips (Frontline Opiate test strips).¹⁷ Permission was obtained from the Head of the Department of Psychological Medicine unit of Civil Hospital Karachi and Arshi Hospital Karachi for the clinical trial. Written consents were obtained from all patients for this study that required an abrupt withdrawal from opioids after admission to the hospital. The patients were divided into 2 groups. Each group comprised of 20 opiate addicts. One group was treated with verapamil and the other group was treated with amitriptyline. The patients received single blind placebo capsule orally during day 1 and day 2 of admission. Single blind treatment with verapamil (40mg TDS) and amitriptyline (10mg TDS) was given from day 3 to day 9 of admission. From day 2 to day 10 of admission, the patients were observed and rated for the presence or absence of opioid withdrawal signs and symptoms experienced during the previous 24 hours. Urine samples were collected on day 1, 5 and 10 of admission and tested immediately for opioids by test strips. Patients were discharged when they were experiencing minimal or no withdrawal symptoms. Total period of study was six months. Data was statistically evaluated by using SPSS version ¹⁶.

RESULTS:

All patients had subjective symptoms and objective signs of opiate withdrawal and urine specimens showing positive results when tested with frontline opiates dipsticks. During the study it was observed that subjects on verapamil treatment, showed no adverse effects that were not attributable to mild opioid withdrawal; on the other hand the adverse drug effects observed with amitriptyline group were dry mouth (15%), blurring of vision (5%), orthostatic hypotension (5%) and headache (10%). The results in figures show the cumulative scores of opiate withdrawal signs and symptoms on day 2 to day 10 of admission. The degree of withdrawal signs and

symptoms was assessed according to the scoring system described in materials and methods.

Group I: Twenty patients were given a placebo treatment on day 1 and day 2 of admission. Thereafter from day 3 to day 9 of admission the patients received 40 mg of verapamil orally three times daily. Diazepam 5 mg for night time sedation and aspirin 300 mg three times a day for muscle pain were used by seven patients on treatment days 1 and 2 of therapy that is days 3 and 4 of hospitalization. Placebo had no significant effects on the cumulative scores of symptoms of acute withdrawal from opioids. A mean score of 17.25 ± 0.781 was obtained on day 2 of admission, which increased to a peak of 31.1 ± 0.777 on day 3 of admission (Figure 1a). Similarly placebo had no significant effects on the cumulative scores of signs of acute withdrawal from opioids. A mean score of 5.4 ± 0.319 was obtained on day 2 of admission, which increased to a peak of 10.20 ± 0.236 on day 3 of admission (Figure 1b).

Group II: Twenty patients were given a placebo treatment on day 1 and day 2 of admission. Thereafter from day 3 to day 9 of admission the patients received 10mg of amitriptyline orally three times daily. Diazepam 5mg for night time sedation, aspirin 300 mg three times a day for muscle pain, intravenous dextrose 5%1000cc/day for anorexia, promethazine (phenergan) 5 mg three times a day for vomiting and hyoscine (buscopan) 10 mg three times a day for abdominal cramps were given to thirteen of the patients on treatment days 1, 2 and 3 of therapy that is days 3, 4 and 5 of hospitalization. A mean score of 14.65 ± 0.658 was obtained on day 2 of admission, which increased to a peak of 31.25 ± 0.627 on day 3 of admission (Figure- 2a). A mean score of 5.55 ± 0.303 was obtained on day 2 of admission, which increased to a peak of 10.95 ± 0.343 on day 3 of admission (Figure 2b). Placebo had no significant effects on the cumulative scores of signs of acute withdrawal from opioids. The amitriptyline group in comparison to verapamil group showed more severe withdrawal symptoms during the entire regimen (Figures 1a, 2a, 3a). On day 4 to 10 of admission the mean score of opiate withdrawal symptoms in verapamil treatment group were 16.7 ± 0.567 , 13.1 ± 0.510 , 7.65 ± 0.326 , 3.5 ± 0.320 , 1.25 ± 0.099 , 0.85 ± 0.131 , 0.1 ± 0.1 whereas in amitriptyline group the mean score of opiate withdrawal symptoms were 30.85 ± 0.616 , 28.65 ± 0.519 , 25.95 ± 0.336 , 15.0 ± 0.205 , 12.05 ± 0.419 , 7.35 ± 0.254 , 6.95 ± 0.234 . From day 4-day 10 statistical evaluation showed highly significant results ($P < 0.001$). Similarly the amitriptyline group in comparison to verapamil group showed more severe withdrawal signs during the entire regimen (Figures 1b, 2b, 3b). On day 4 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 4.6 ± 0.265 whereas in amitriptyline group the mean score of opiate withdrawal signs was 10.20 ± 0.286 . On day 5 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 2.9 ± 0.289 where as in amitriptyline group the mean score of opiate withdrawal signs was 8.95 ± 0.825 . On day 6 of admission the mean score of opiate withdrawal signs in verapamil treatment group was 1.5 ± 0.223 whereas in

amitriptyline group the mean score of opiate withdrawal signs was 6.15 ± 0.587 . On day 7 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 4.85 ± 0.149 . On day 8 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 2.7 ± 0.206 . On day 9 of admission the mean score of opiate withdrawal signs in verapamil treatment group was zero (0) where as in amitriptyline group the mean score of opiate withdrawal signs was 1.1 ± 0.216 . On day 10 of admission the mean score of opioid withdrawal signs in verapamil treatment group was zero (0) whereas in amitriptyline group the mean score of opiate withdrawal signs was 1.05 ± 0.223 . The effects of verapamil to decrease the signs of acute withdrawal from opiates when compared with amitriptyline from day 4 to day 10 of the admission were highly significant ($P < 0.001$)

Figure: 1a

Effects of Verapamil treatment on subjective symptoms of acute withdrawal from opioids

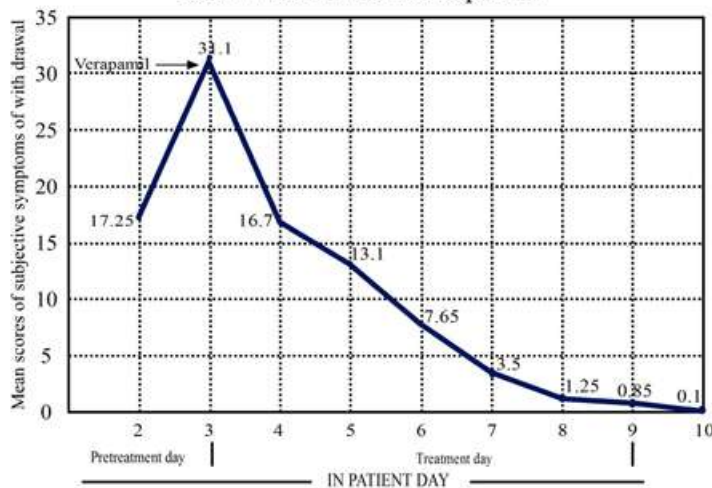


Figure: 1b

Effects of Verapamil treatment on objective signs of acute withdrawal from opioids

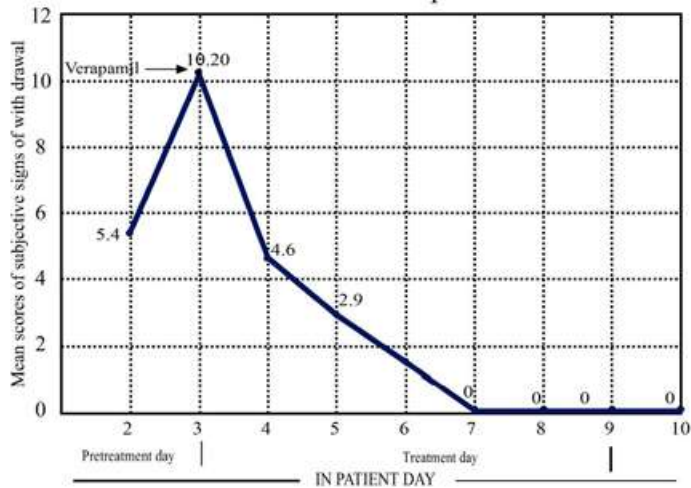


Figure: 2a

Effects of Amitriptyline treatment on subjective symptoms of acute withdrawal from opioids

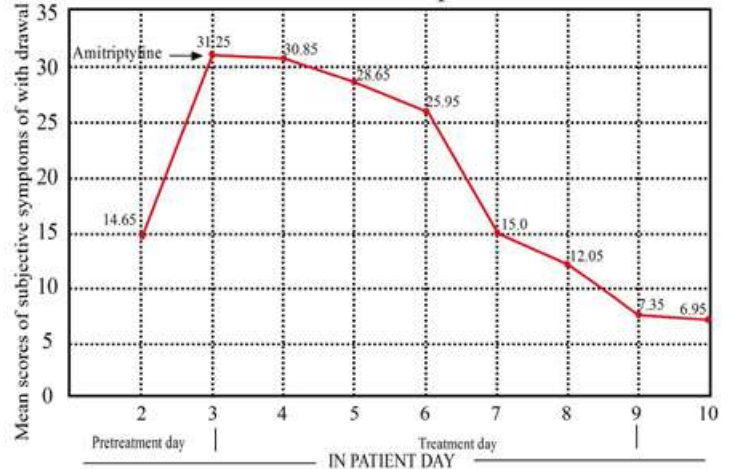


Figure: 2b

Effects of Amitriptyline treatment on objective signs of acute withdrawal from opioids

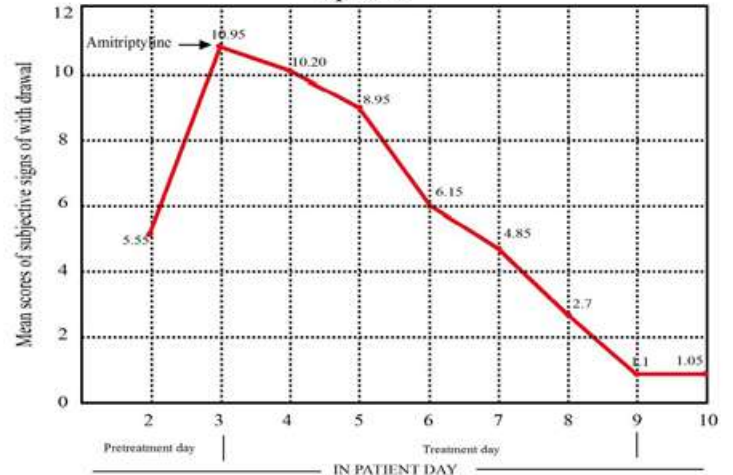


Figure: 3a

Comparison of effects of treatment with Verapamil and Amitriptyline on subjective symptoms of acute withdrawal from opioids

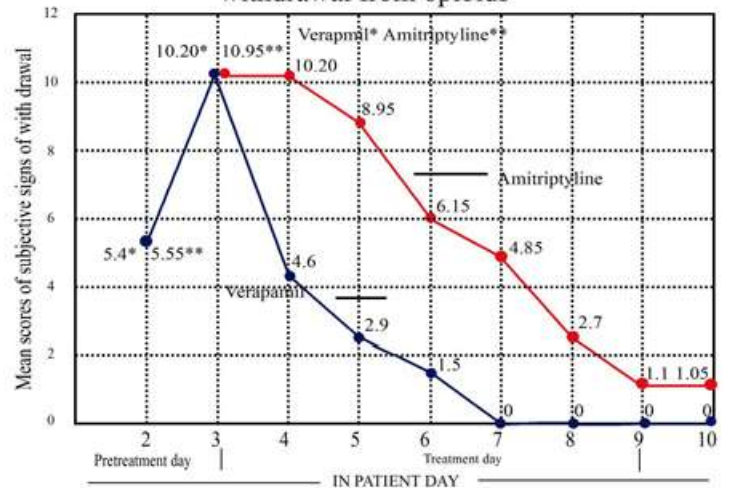
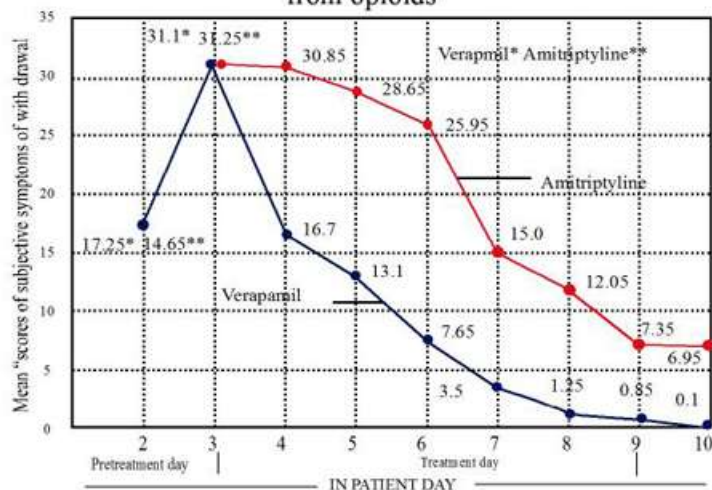


Figure: 3b
Comparison of Effects of Treatment with Verapamil and Amitriptyline on objective signs of acute withdrawal from opioids



DISCUSSION:

A study was conducted by Baloch¹⁸ and Mahesar¹⁹ on role of verapamil in opioid dependence in guinea-pigs in vivo and in vitro in the department of Pharmacology and Therapeutics BMSI, JPMC, Karachi. Their observations showed a highly significant effect of verapamil in vivo and in vitro, which initiated a proposal of conducting a pilot study in opioid addict's hospitalized patients. The purpose of this single blind pilot study was to conduct a clinical trial and to investigate the efficacy of verapamil in acute opioid abstinence syndrome in hospitalized patients. Amitriptyline is in vogue at present in the treatment of opioid abstinence in various hospitals of Karachi. We have compared the therapeutic effect of verapamil with amitriptyline. Verapamil being a safe drug with fewer side effects was used in minimal dose of 40 mg TDS and for short duration. When the data for withdrawal scores for verapamil treatment were statistically evaluated it showed that subjective symptoms and objective signs were significantly reduced from day 3 to day 10 of admission. Our results are compatible with the work of Baloch¹⁸ and Mahesar¹⁹ who observed the effect of verapamil in morphine dependent animals subjected to naloxone in vitro and vivo. They observed that calcium channel blocker was effective in reducing the abstinence in vivo and in vitro effects. Our results are also compatible with the study done by Baeyense¹³ in which verapamil was given to morphine dependent rats intraperitoneally (i.p.) (10, 20 and 40 mg/Kg) and intra-cerebro-ventricularly (i.c.v.) (160µg) 30 minutes and 10 minutes respectively before naloxone challenge. This study showed that verapamil prevented diarrhoea after its i.p. but not after its i.c.v. injection due to its peripheral action and also that verapamil reduced body weight loss and jumping only after its i.c.v. administration due its central action. This study reported that verapamil caused no overt behavioural effects which could have interfered with the expression of the abstinence syndrome. Our results are also consistent with the work of Bongiani¹⁴ who observed withdrawal signs in two different groups of morphine dependent rats injected

with naloxone intraperitoneally. The animals constantly lost approximately 8% of their body weight in 1 hour. Furthermore they displayed diarrhoea, wet dogshakes, agitation, grooming, teeth chattering and lacrimation. The administration of verapamil subcutaneously to morphine dependent rats 20 minutes before naloxone challenge reduced the appearance of most of the behavioral signs of abstinence syndrome. Our results are highly in accordance with the work of Seth et al²⁰ who observed a significant dose-dependent attenuation of naloxone-induced morphine withdrawal syndrome in mice with calcium channel blockers verapamil 20 mg/kg ($P < 0.05$) and diltiazem 30 mg/kg ($P < 0.01$).

Chronic dependence on opioids demonstrated an adaptive increase in number of calcium channels. This increased calcium channels, precipitate in opioid abstinence syndrome. Thus, the signs and symptoms of opioid abstinence syndrome can be attenuated or prevented by administration of calcium channel blockers following opioid withdrawal.²¹ Thus calcium channel blockers may be rational and useful therapeutic agents in clinical management of drug dependence and withdrawal^{22,23,24} especially as they appear to have no significant addicting properties themselves and show anticonvulsant action in condition of central nervous system hyperexcitability, which is a general feature of drug withdrawal²⁵. The other objective of this study was to investigate the efficacy of amitriptyline compared with verapamil. It is obvious from observations that the amitriptyline was not significantly effective in suppressing withdrawal signs and symptoms from day 3 to day 10 of admission. The pattern of withdrawal symptoms and signs in amitriptyline group is not incompatible with a rather ineffective treatment or even simply a placebo effect. When unmodified by treatment the withdrawal syndrome for opiates reached its peak intensity between the 3rd and the 6th day and thereafter, the severity decreased gradually and most of the grossly observable symptoms disappeared in 7 to 10 days.¹¹ This pattern is broadly the same as that shown by amitriptyline group.

CONCLUSION:

Verapamil therapy is safe, effective and more pronounced in treating the acute opioid withdrawal syndrome than amitriptyline in patients with chronic dependence on opioids. This treatment will facilitate opioid addicted patients to directly enter in a maintenance program for detoxification. It may also be of use in preventing the occurrence of the protracted or secondary abstinence syndrome because of possible rapid normalization of opiate system. Comparative studies examining a number of factors, such as patient's compliance, its efficacy in larger groups and its role in detoxification utilizing verapamil and amitriptyline are open venues for future research.

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