Gabapentin in the Management of Pentazocine Dependence: A Potent Analgesic - Anticraving Agent

P Kumar*, MK Jain**

Abstract

Objectives: To evaluate the role of Gabapentin in the management of Pentazocine dependence for suppressing muscle aching and craving during its withdrawal.

Material and Methods: Patients of Pentazocine dependence were divided in two groups GpA and GpB (n=10 in each) and were administered Clonidine (P.O.) in first seven days (acute detoxification phase) and later Naltrexone (P.O.) from seventh day onwards (stabilisation-maintenance phase). Gabapentin (1200 mg/day) was additionally added in group B. Muscle pain and craving were rated on 100 mm visual-analogue scale. Psychological dependence was assessed on four step categorical scale.

Results: Group B (Gabapentin group) scored significantly lower (p<0.001) than group A on both the parameters. Psychological dependence was significantly low (p<0.01) in Gabapentin group.

Conclusion: Gabapentin is an important adjuvant to the management of opiate dependence both in acute detoxification as well as stabilisation phase.

INTRODUCTION

Pentazocine (Fortwin), an opioid analgesic is a κ-receptor agonist and induces spinal analgesia. It is easily manageable over-the-counter and is one of the major substance abuse disorders in this region. Its acute withdrawal symptoms viz. abdominal cramps, anxiety, tremulousness, lacrimation, vomiting, nagging muscle aches and craving further reinforce dependence. Clonidine, an antihypertensive agent, is frequently recommended for acute detoxification of opioids and significantly blocks majority of symptoms.1 It aids to smooth stabilisation of patients on Naltrexone for maintenance therapy. Naltrexone, an opioid agonist-antagonist is widely used in large dosage (100 mg/day, build up gradually) to prevent euphorigenic effects of opioids. A combination therapy of Clonidine - Naltrexone was proposed in the management of opioid dependence.2

However, Clonidine is least effective in suppressing withdrawal-induced muscle aching and craving3 and emerged out as important factor for relapse. Pain is a suffering, which includes original pain sensation with evoked reaction. It is not only determined by peripheral stimulation but also by information travelling from brain to spinal cord as narrated by Gate-Control theory.4 Anti-prostaglandins are least effective in pain of neuropathies and non-inflamed tissue.5 Ample evidences have given to believe that Gabapentin, an anticonvulsant has potent analgesic effect in various neuropathic painful conditions.6-8 It has also revealed anticraving effects in cocaine9 and alcohol withdrawal.10

The present study was therefore an attempt to explore the possible role of Gabapentin in the management of Pentazocine dependence with reference to its withdrawal induced muscle aching and craving.

MATERIAL AND METHODS

This was an in-patient three weeks study in the subjects abusing ampoules Pentazocine (1 amp = 30 mg), 6-10/day IV, SC, or IM without abstinence during past one month.

Inclusion Criteria: Patients fulfilling the criteria of opiate dependence according to DSM IV11, at least one episode of opiate withdrawal before one month fulfilling DSM IV criteria and consent, both for the study and HIV screening.

Exclusion Criteria: Substance abuse other than pentazocine, gross physical illness, other neuropsychiatric illness in present or past or in family.

The sample of the study (n=20) was divided into group A and Group B, 10 in each. Pentazocine was stopped abruptly in both the groups.

Group A received Tab. Clonidine P.O. 0.1 mg thrice daily in fixed dose schedule from day 1 to day 7 and Tab. Naltrexone (50 mg BD) from day 7 to day 21, gradually built up in two
days.

Group B: In addition to treatment regimen identical to GpA, group B received caps Gabapentin, (300 mg), 2 X BD (1200 mg/day) from day 1 to day 21 as an add-on therapy.

Permissible Treatment: Tab. Lorazepam, Nitrazepam for insomnia, atropine and normal saline for bradycardia and hypotension respectively.

Investigation: Besides routine blood-urine analysis, blood sugar and hepatic and renal function tests, all the patients were screened for Hepatitis B and HIV (after obtaining pretreatment consent).

Assessment: Visual analogue scale 100 mm, already administered by investigator, was administered on day 0 (24 hours after abrupt withdrawal), day 7, 14 and 21 for rating the muscle pain and craving for pentazocine.

Psychological dependence was assessed by a four step categorical scale.

Score 0: No desire for substance; Score 1: Thinks that substance would be pleasurable but decides against taking it; Score 2: Obvious desire for substance but the intake can be deferred; Score 3: Overwhelming desire leading to the impulsive use.

Statistical analysis was done using ‘t’ test and Chi-square test.

RESULTS

Patients blood, urine examination, renal and hepatic function tests were within normal limit. All the subjects were negative to hepatitis B and HIV. Mean age of both the groups A (37 ± 4) and group B (34 ± 6) was similar and is not going to affect results.

Pain Score (Fig. 1): The pain score in group B on day 7 (20.5 ± 5.98) was significantly (p< 0.001) lower than group A (62.5 ± 5.89) and indicates significantly greater reduction in pain (79.5%) by Gabapentin as compared to Clonidine alone (37.5%).

A significant (p< 0.01) decline in pain score in Group A from day 7 (62.5 ± 5.89) to day 21 (54 ± 5.67) indicate reduction in pain in the Naltrexone group. Similarly a further decline (p< 0.05) in pain scores was observed from day 7 (20.5 ± 5.98) to day 21 (12.5 ± 2.29) in Group B. However the end-point scores were significantly (p< 0.001) lower in Group B (12.5 ± 2.29) as compared to Group A (54 ± 5.67) and reflects potent synergistic effect of Gabapentin with Naltrexone in inducing analgesia.

Craving Score (Fig. 2): Patients of Group B (52 ± 9.77) scored significantly (p<0.001) less than Group A (80 ± 7.45) on Day 7 and indicates that Gabapentin has potential anticroaving effect pre se unlike Clonidine.

Naltrexone also significantly (p<0.001) decreased the craving scores from day 7 (80 ± 7.45) to 21 (34 ± 5.67). However the decline became significantly (p<0.001) steeper in Group B from day 7 (52 ± 9.77) to Day 21 (11 ± 3.94), when Gabapentin was added. The end-point scores were significantly (p<0.001) lower in Group B (11 ± 3.94) than Group A (34 ± 5.67).

Psychological Dependence (Fig. 3): The psychological dependence was identical in both the groups in pretreatment phase (score-3). However the scores were significantly (p< 0.001) lower at the end of third week in Group B as compared to Group A.
to Group A. Higher number of patients in Group B (70%) scored ‘0’ than Group A (50%) and had no desire at all. On the other hand, on score 1 and score 2 category, number of patients were less in group B (30% and 0%) as compared to Group A (40% and 10%) respectively.

**DISCUSSION**

Pentazocine was suddenly withdrawn in all the patients as the outcome was similar in abrupt and gradual opiate detoxification groups.\(^1\)

The study could have been more scientific, had the effect of Gabapentin monotherapy on aforesaid parameters been compared with placebo controlled groups. Owing to ethical issues, both the groups A and B received Clonidine and Naltrexone for acute detoxification and stabilisation maintenance phase respectively and Gabapentin as add on therapy in Group B.

Gabapentin significantly (p< 0.001) decreased muscle aching (79.5%) than Clonidine (37.5%) on day 7. No tolerance to analgesic effect was observed by the end of third week. Although Clonidine plays a potential role in ameliorating various opiate withdrawal symptoms,\(^1\) yet it is least effective in suppressing opiate withdrawal muscle aching\(^1\) as also observed by us. Moreover, a rapid development of tolerance to analgesic effect of Clonidine was also reported in experimental studies.\(^16\)

Role of Gabapentin in the management of certain painful ailments viz. neuropathic pain, post-herpetic and glossopharyngeal neuralgia\(^6-8\) is well documented. However exact mechanism of opiate withdrawal muscle aching and its amelioration by Gabapentin could not be commented and needs further exploration. Gabapentin seems to have unique effect on voltage dependent Ca channel currents at postsynaptic dorsal-horn neurons and could interrupt processing of pain.\(^6\) Yet another possibility could be induction of various neurotransmitter receptor supersensitivity. K-receptors subsensitivity and activation of endogenous opiate antagonist during the state of dependence,\(^3\) which may be responsible for muscle aching during withdrawal phase and effect of Gabapentin on central neuroplasticity and neuromodulation in ameliorating it.

Gabapentin further reduced the pain from day 7 to day 21 when added with Naltrexone and may have synergic analgesic effect with a weak agonist-antagonist Naltrexone. A synergistic effect of Gabapentin to opiate agonist was also reported in cancer pain\(^17\) and supports our finding. Mild analgesic effect observed at the end of third week in Naltrexone group could either be due to alteration in the perception of pain per se or neuroadaptation at central κ-receptor. DA receptor, reactivation of endogenous enkephalins and attenuation of activated endogenous opiate antagonist following three weeks abstinence.

Blocking of withdrawal craving by Gabapentin was a serendipitous finding and was not shared by Clonidine.\(^3\) Such an aid by Gabapentin to clonidine-detoxification regime could be of great clinical relevance in the management of opioid dependence.

Naltrexone per se (GpA) showed anticraving effects both on day 14 and day 21. However add-on therapy with Gabapentin (GpB) significantly potentiated this effect on corresponding days and further speaks its potent anticraving effect. Moreover, psychological dependence was also significantly less in Gabapentin- combination group than Naltrexone alone.

Anticraving effect of Naltrexone is presumed to be on cognitive basis as patients are aware of blocking “Highs” by it.\(^3\) On the other hand, mechanism for anticraving effects of Gabapentin may be manifolds. It has potential role in the management of bipolar-affective disorder,\(^18\) anxiety, depression,\(^19\) mood-irritability and behavioural dyscontrol.\(^20\) Subtle mood dysregulation is thought to be a part of a “protracted withdrawal syndrome”. These lingering residual deficits respond dramatically to narcotics and is an important cause of relapse. The stabilising effect of Gabapentin on these parameters may explain its therapeutic efficacy in blocking opiate craving. The role of Gabapentin in reducing Cocaine withdrawal\(^8\) craving was also reported. The rise in dopamine by cocaine is thought to underlie the reinforcement behaviour of cocaine. Gabapentin significantly reduces the cocaine induced increase in dopamine and thus appears to decrease craving.\(^9\) Since chronic opiate exposure also induces supersensitivity of several neurotransmitter circuits including dopaminergic system,\(^3\) their central neuromodulation by Gabapentin could also explain its anticraving effects for opiates as observed by us and needs further investigations.

High rate of recurring dependence in opiate addict is often a frustrating experience both for the family and therapist. In these situation one must try and do the best one can. It is therefore tempting to propose a treatment modality comprising of Gabapentin-clonidine combination in acute detoxification phase (0-7 days) and Gabapentin-Naltrexone combination in stabilisation-maintenance phase (7th day onwards). It is our contention that Gabapentin-Naltrexone combination may prove an important adjuvant to relapse prevention strategies in ‘protracted abstinence syndrome’ and needs long term followup studies. Its favourable side effects profile with lack of hepatotoxicity and interactions with other drugs warrants additional controlled studies on other opiates too viz. Morphine, Heroin etc.

**REFERENCES**

5. Ramdell, LO, Selitto JJ. A method for measurement of
analgesic activity on inflamed tissue. *Arch Int Pharmacodyn Ther* 1957;111:409-19.


