

Trigeminal Neuralgia and role of NMDA antagonists –Memantine along with TRPV1 agonists in an animal model of pain

Kalra J, Dhasmana DC, Sharma T

ABSTRACT

Background: Neuropathic pain involves both functional and structural alterations in the nervous system which makes it very difficult to treat, and none of the currently available drugs offer a satisfactory cure.

Aim: To study the role of memantine (NMDA antagonist) and capsaicin (TRPV1 antagonist) in an acute model of neuropathic pain in rats.

Methods: Animals were divided into three groups of 6 animals each. The first group received carbamazepine, the second group received memantine while the third group received oral memantine and topical capsaicin. Neuropathic pain was induced by instilling a drop of 5M NaCl solution on the surface of the cornea in the test eye and then the number of eye wipes performed with ipsilateral forepaw was counted for a period of 30seconds.

Results: All three treatment categories, i.e. carbamazepine, memantine and memantine plus capsaicin group showed significant analgesia when compared to the control eye ($p < 0.05$).

Conclusion: Use of memantine alone or in combination with capsaicin may break the self-perpetuating cycle of neuropathic pain at the very outset and prevent the recruitment of more and more neurons that are responsible for the prolonged pain in neuropathies due to central sensitization.

Key words: memantine, capsaicin, neuropathic pain, neuralgia

INTRODUCTION

Glutamate (Glu) is a major excitatory neurotransmitter in the mammalian central nervous system, acting both at ligand-gated (ionotropic) ion channels and G-protein-coupled metabotropic receptors. Ionotropic receptors are subdivided into NMDA (glutamine-N-methyl-D-aspartic acid) and non-NMDA [α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid] receptors. However, only NMDA receptors are found within trigeminal ganglion cells.¹

Trigeminal neuralgia (Tic douloureux) (TGN) is characterised by sudden severe brief episodes of recurrent stabbing pain in the distribution of one or more branches of the fifth (trigeminal) cranial nerve. It is relatively rare and the majority of cases present unilaterally. The generally accepted common cause is compression of the Gasserian ganglion (sensory ganglion of the trigeminal nerve) or its branches by a blood vessel. The mainstay of pharmacological management is carbamazepine. Pain relief is seen in one of every two cases. Oxycarbazepine can also be used. Baclofen has

been reported as efficacious; however a Cochrane review concluded insufficient evidence to support it as a unimodal treatment for TGN. Gabapentin, pregabalin, topiramate and older anticonvulsants have also been used in refractory cases but with varying degree of success.¹

Recently NMDA receptor antagonists have been explored for analgesia in selected situations. Adverse drug consequences of ketamine, an NMDA receptor antagonist have limited their use. But certain low affinity NMDA antagonists like CHF3381 have shown promising results in animal studies with better tolerability and fewer adverse drug reactions, thus opening up this field for future research.^{2,3}

The purpose of our study was to observe the analgesic effect of memantine that shows fast blocking and unblocking kinetics and to also analyze if its combination with capsaicin offers any additional advantage.

MATERIAL AND METHODS

The study was conducted after clearance from

Institutional Animal Ethics Committee. Materials: NaCl solution-5 M NaCl solutions for topical application in the test eye and 0.15M solution for application in control eye. Memantine was obtained from Sun Pharmaceuticals and Capsaicin was obtained from Shalaks Pharmaceuticals, India. Methods: Animals were divided into three groups of 6 animals each. First group received carbamazepine (positive control) intraperitoneally; second group received memantine orally; and the third group received both memantine orally and capsaicin (topically in the region around mouth and on the face medial to the ear and beneath the eyes). The animals were kept under standard laboratory conditions with access to food and water ad libitum. Neuropathic pain was induced by instilling a drop of 5M NaCl solution on the surface of the cornea in the test eye using a fine dropper and then the number of eye wipes performed with ipsilateral forepaw was counted for a period of 30 seconds. While in the control eye, a drop of 0.15M NaCl solution was applied topically.³ These drugs were administered 30 minutes prior to inducing neuropathic pain. Number of eye wipes was counted in test eye before and after giving the drug. A reduction in the number of eye wipes was taken as an indicator of analgesia.

Statistical analysis: Two-way repeated ANOVA was done for intergroup comparisons and for repeated measures in the same group, since each animal acted as its own control. As the response was measured in terms of number of eye wipes, square root transformation was used to fulfill the assumption of ANOVA using quadratic trend. Groups showing $p < 0.05$ were considered to have achieved significant analgesia

RESULTS

All three treatment categories, i.e. Carbamazepine, Memantine and Memantine plus Capsaicin showed significant analgesia ($p < 0.05$). (Table 1 and 2) Within the treatment groups i.e. Carbamazepine, Memantine and memantine plus Carbamazepine the difference was insignificant.

This would mean that memantine as well as memantine and Carbamazepine produced analgesia as comparable to Carbamazepine, the positive control in our study. Hence it may be deduced that memantine and memantine plus carbamazepine combination produced significant analgesia.

Table 1: Two-way repeated ANOVA for Intergroup comparisons

Tests of Within-Subjects; Contrasts Measure: eye wipes

Source	Day	Type III Sum of Square	Df	Mean Square	F	Sig.
Day	Linear	600.250	1	600.250	666.944	.000
	Quadratic	2196.009	1	2196.009	666.954	.000
Day*	Linear	12.250	5	2.450	2.722	.083
	Quadratic	21.713	5	4.343	1.319	.331
Day * Treat	Linear	6.000	2	3.000	3.3330	.078
	Quadratic	45.852	2	22.926	6.963	.013
Error(Day)	Linear	9.000	10	0.900		
	Quadratic	32.926	10	3.293		

Table 2: Tests of Between-Subjects Effects Measure: eye wipes; Transformed Variable: Average

Source	Type III Sum of Square	Df	Mean Square	F	Sig
Rep	13.648	5	2.730	.788	.581
Treat	12.259	2	6.130	1.770	.220
Error	34.630	10	3.463		

DISCUSSION

In our study we used the acute model of trigeminal pain. The combination of capsaicin and memantine as well as memantine alone produced significant analgesia when compared to control group as well as the pre-treatment group ($p < 0.01$). Carbamazepine was used as a positive control in our study, and as documented in earlier studies, it produced significant analgesia.⁴

Whenever peripheral nerves are stimulated, the nociceptive neurons initially release glutamate but on long term or prolonged stimulation, other

neurotransmitters like cGRP, neurokinin A, somatostatin etc. are also released which can lead to increased spinal excitability. It has been documented in earlier studies that NMDA receptors are upregulated in neuropathic pain syndromes.^{5,6} In complex regional pain syndromes, there may be enlarged somatotropic reorganization of the painful limb leading to an exaggerated pain perception. So we anticipated that the use of NMDA antagonists will relieve pain by central mechanism.

Memantine is a non-competitive NMDA receptor antagonist that exhibits fast blocking and unblocking kinetics, and is more effective and better tolerated than other high affinity NMDA antagonists like ketamine and amantadine.^{6,7} It decreases the firing rate of neurons and works on central pain mechanisms.⁴ In our study, the group receiving only memantine showed significant analgesia. It is postulated that memantine, like CHF 3381, may also inhibit the “wind up” phenomenon which is characterized by an increased excitability of dorsal horn neurons due to repeated stimulation of type C nerve fibers.⁸ Therefore, cumulative amplitude of depolarization may have decreased the amplitude of nociceptive fibers leading to an analgesic response in our study.⁹ The wind-up phenomenon is complex and involves more neurotransmitters besides glutamate.^{9,10} Hence, blockade of TRPV1 receptors by capsaicin may improve the analgesic response of memantine by inhibiting the release of bradykinin and prostaglandins and other downstream processes that activate phospholipase C pathway and perpetuate pain.

The nociceptive neurons of peripheral nervous system have TRPV1 receptors and these receptors are involved in modulation and integration of various painful stimuli in both the central nervous system as well as in the peripheral nervous system. However, earlier studies of use of capsaicin in animal models have shown that it may cause hyperalgesia on initial application but repeated

application may lead to analgesia due to functional and physiological desensitization. Therefore, we expected that when capsaicin and memantine are given in combination, the consequences could range from hyperalgesia to analgesia.¹¹ However, our study revealed that the combination sustained the analgesic effect of memantine rather than causing hyperalgesia. The sustained analgesia may be an indirect indicator of the fact that this combination may offer the advantage of freedom from tolerance to beneficial effect of memantine, and more importantly may prevent central sensitization by acting on mechanisms other than those modulated by NMDA receptors. Recent studies substantiate our findings wherein it is suggested that hyperalgesia and allodynia are sensitive to NMDA receptor antagonism and hence this combination can nullify the initial hyperalgesia of capsaicin.¹²

CONCLUSION

Memantine alone as well as the combination of memantine and capsaicin produced significant analgesia comparable to carbamazepine. However, the long term benefit of these drugs in preventing perpetuation of pain needs to be confirmed in animal models of chronic pain.

ACKNOWLEDGEMENT

We acknowledge the help of the Research Committee, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun for providing financial grant to support this research work.

AUTHOR NOTE

Juhi Kalra, Associate Professor, Contact- 9412053770, Email- drjuhi9@gmail.com
(Corresponding Author)

D C Dhasmana, Professor

Taruna Sharma, Professor

Department of Pharmacology, Himalayan Institute of Medical Sciences, HIHTU, Dehradun

REFERENCES

1. Piovesan EJ, Randunz V, Utiumi M, Lange MC, Kowacs PA, Mulinari RA, et al. Influence of NMDA and non-NMDA antagonists on acute and inflammatory pain in the trigeminal territory: a placebo control study. *Arq Neuropsiquiatr*. 2008 Dec;66(4):837-43.
2. Villetti G, Bergamaschi M, Bassani F, Bolzoni PT, Maiorino M, Pietra C, et al. Antinociceptive activity of the N-methyl-D-aspartate receptor antagonist N-(2-Indanyl)-glycinamide hydrochloride (CHF3381) in experimental models of inflammatory and neuropathic pain. *J Pharmacol Exp Ther*. 2003 Aug;306(2):804-14.
3. Tamaddonfard E, Khalilzadeh E, Hamzeh-Gooshchi N, Seiednejhad-Yamchi S. Central effect of histamine in a rat model of acute trigeminal pain. *Pharmacol Rep*. 2008 Mar-Apr;60(2):219-24.
4. Sinis N, Birbaumer N, Gustin S, Schwarz A, Bredanger S, Becker ST, et al. Memantine treatment of complex regional pain syndrome: a preliminary report of six cases. *Clin J Pain*. 2007 Mar-Apr;23(3):237-43.
5. Krystal JH, D'Souza DC, Petrakis IL, Belger A, Berman RM, Charney DS, Abi-Saab W, Madonick S. NMDA agonists and antagonists as probes of glutamatergic dysfunction and pharmacotherapies in neuropsychiatric disorders. *Harv Rev Psychiatry*. 1999 Sep-Oct;7(3):125-43.
6. Beal MF, Hauser SL. Trigeminal neuralgia, Bell's palsy and other cranial nerve disorders. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL (editors). *Harrison's Principles of Internal Medicine*. 16th ed. New York: Mc Graw-Hill Companies, Inc; 2005:2434-8.
7. Kenins P. Responses of single nerve fibres to capsaicin applied to the skin. *Neurosci Lett*. 1982 Mar 17;29(1):83-8.
8. Parsons CG. NMDA receptors as targets for drug action in neuropathic pain. *Eur J Pharmacol*. 2001 Oct 19;429(1-3):71-8.
9. Thompson SW, Gerber G, Sivilotti LG, Woolf CJ. Long duration ventral root potentials in the neonatal rat spinal cord in vitro; the effects of ionotropic and metabotropic excitatory amino acid receptor antagonists. *Brain Res*. 1992 Nov 6;595(1):87-97.
10. Begon S, Pickering G, Eschaliere A, Dubray C. Magnesium and MK-801 have a similar effect in two experimental models of neuropathic pain. *Brain Res*. 2000 Dec 29;887(2):436-9.
11. Winter J, Bevan S, Campbell EA. Capsaicin and pain mechanisms. *Br J Anaesth*. 1995 Aug;75(2):157-68.
12. Quartaroli M, Carignani C, Dal Forno G, Mugnaini M, Ugolini A, Arban R, et al. Potent antihyperalgesic activity without tolerance produced by glycine site antagonist of N-methyl-D-aspartate receptor GV196771A. *J Pharmacol Exp Ther*. 1999 Jul;290(1):158-69.