Pregabalin In The Treatment Of Peripheral Neuropathic Pain: Theoretical Assumptions And Clinical Practice

A Cinetto, E Ferrulli, G Venier

Citation

A Cinetto, E Ferrulli, G Venier. *Pregabalin In The Treatment Of Peripheral Neuropathic Pain: Theoretical Assumptions And Clinical Practice*. The Internet Journal of Anesthesiology. 2006 Volume 11 Number 2.

Abstract

The aim of this study is to verify the effectiveness and safety of Pregabalin in the treatment of chronic peripheral neuropathic not oncological pain. 33 patients aged 58 ± 13 have been studied with average age of 58 years. The therapy effectiveness was evaluated with VAS scales and Karnofsky performance status index at the beginning, at the end of therapy and at 2 months after drug suspension. It was used at a dosage of 150-600 mg/die according to the response and collateral effects. 36% (C.I. 22% - 53%) of the patients have abandoned the therapy for collateral effects. The pain relief is turned out statistically significant both at the end of the therapy and in the follow up. Conclusions: Pregabalin turns out effective in the treatment of the neuropathic pain with stabilized effects. The treatment is burdened by a high incidence of collateral effects (36% (22%-53%)) and consequent abandonment of the therapy.

INTRODUCTION

Neuropathic pain originates from a dysfunction or a damage of the central or peripheral nervous system[1,2]. According to the site of the lesion in the nervous system the neuropathic pain can be classified as central or periferic[2]. Clinically neuropathic pain is characterized as chronic course, is described by the patients as lancinating, burning, accompanied by smart, electric shock, pins and needles and paresthesia[2,4]. Pain can be spontaneous or provoked, with evocation of allodynia and/or hyperalgesia. Neuropathic pain can be serious and invalidating; it may and compromise the life quality with interference on the sleep and humor[3]. Peripheral neuropathic pain includes diabetic neuropathy, trigeminal neuralgia, post-herpetic neuralgia, reflex sympathetic dystrophy, post laminectomy syndrome, post-entrapment syndrome, ghost limb syndrome, radiculitis and entrapment neuropathies. Pregabalin (the S-3-aminometil-5acido-metilesanoic) has anticonvulsive and analgesic activity; studies in vitro and experimental models show that pregabalin is a selective binder with high affinity[11]to voltage dependent calcium channels X receptors 2 - in the SNC[5,6,8]; such connection reduces the depolarization induced from the income of calcium and diminishes the release of neurotransmitters (noradrenalin, glutamate, substance-P) in the hyper excited neurons[5,6,12,13]. Pregabalin prevents the reactions to pain in neuropathic pain animal models, even in allodynia and hyperalgesia[7,8].

Pregabalin is indicated in the treatment of peripheral neurophatic pain.

AIM OF THE STUDY

The aim of the study is the evaluation of the effectiveness and safety of Pregabalin for treatment of chronic peripheral neuropathic not oncological pain in adults.

MATERIALS AND METHODS

Criteria of inclusion: aged between 18 and 80 years, presence of not oncologic peripheral neuropathic pain. Criteria of exclusion: hypersensitivity versus Pregabalin, pregnancy, renal insufficiency, alcohol poisoning, use of psychotropic drugs, use of drugs commonly used in the neuropathic pain (antiepileptics, benzodiazepines, gabapentin, tricyclics, etc.). All patients were informed and signed per consensus as italian legislative dispositions prescribed. The basal evaluation card compilation has taken in consideration: patient's age, pathology and type of pain, symptoms and signs of peripheral neurosuffering at the beginning and at the end of therapy cycle with the Pregabalin, the analgesic therapy at the beginning of the study, the VAS (Visual Analogue Scales) [9] and Karnofsky Performance Status [9] at the beginning of the therapy, at the term of 12th week of therapy and 2 months from the suspension of the drug. The selected patients were submitted to a cycle of therapy with Pregabalin at a flexible dosage of

150-600 mg/die in two every day administrations; such posologic regimen has turned out to be more favourable at fixed dose in terms of tolerability and individual answer [4]. We started with 150 mg/die and we increased the dosage up to 300-600 mg/die weekly based on the therapeutic answer and collateral effects; the therapeutic dosage was continued for 12 weeks; it was moreover made a control at a distance of 2 months from the drug administration term. The design of the study is represented in fig. 1.

Figure 1

Figure 1

150 mg/die First week	300 mg/die Second week	600 mg/die third week	Therapy monitoring 4th – 12th week	check at 2 months from the suspension of therapy

RESULTS

The studied population was of 33 patients, 60.6% (n=20) of feminine sex, 39.4% (n=13) male; the average age is of 58,87 years with standard deviation of 13,83, median of 64 and mode of 69; range of age from 27 years to 76 (Tab1).

Figure 2

Table 1

AGE

N	Valid	33
	Missing	0
Mean		58,8788
Median		64,0000
Mode		69,00
Std. Deviation		13,82877
Skewness		-,607
Std. Error of Skewness		,409
Kurtosis		-,720
Std. Error of Kurtosis		,798
Minimum		27,00
Maximum		76,00

64% of the patients (n=21) recruited have finished the study protocol, while 36% (n=12) (C.I. 22% - 53%) have interrupted the assumption of the Pregabalin. The subclass of pathologies with peripheral neuropathic pathology treated have been: lower back pain (n=10), diabetic neuropathy (n=2), vertebral cervical pain (n=2), vertebral crack (n=2), ghost limb syndrome (n=1), coccyx pain (n=1), post-herpetic neuralgia (n=1), trigeminal neuralgia (n=1) and anal pain (n=1). Because the distribution of the values of VAS and Karnofski performance status (KPF) wasn't normal, we have used non parametric tests for the statistical analysis: Wilcoxon rank test and the sign test (Tab 2, 3, 4, 5).

Figure 3

Table 2

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
VASSETT - VASINIZI	Negative Ranks	19	10,00	190,00
	Positive Ranks	0	,00	,00
	Ties	2		
	Total	21		

a VASSETT < VASINIZI
b VASSETT > VASINIZI
c VASINIZI = VASSETT

Test Statistics

	VASSETT - VASINIZI
Z	-3,848
Asymp. Sig. (2-tailed)	,000
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Based on positive ranks.
b Wilcoxon Signed Ranks Test

Sign Test

Frequencies

		N
VASSETT - VASINIZI	Negative Differences	19
	Positive Differences	0
	Ties	2
	Total	21

a VASSETT < VASINIZI
b VASSETT > VASINIZI
c VASINIZI = VASSETT

Test Statistics

	VASSETT - VASINIZI
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Binomial distribution used.
b Sign Test

Legenda: VASSETT = VAS after a week therapy
VASINIZI = initial VAS

Figure 4

Table 3

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
VASCONTR - VASINIZI	Negative Ranks	15	8,00	120,00
	Positive Ranks	0	,00	,00
	Ties	6		
	Total	21		

a VASCONTR < VASINIZI
b VASCONTR > VASINIZI
c VASINIZI = VASCONTR

Test Statistics

	VASCONTR - VASINIZI
Z	-3,420
Asymp. Sig. (2-tailed)	,001
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Based on positive ranks.
b Wilcoxon Signed Ranks Test

Sign Test

Frequencies

		N
VASCONTR - VASINIZI	Negative Differences	15
	Positive Differences	0
	Ties	6
	Total	21

a VASCONTR < VASINIZI
b VASCONTR > VASINIZI
c VASINIZI = VASCONTR

Test Statistics

	VASCONTR - VASINIZI
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Binomial distribution used.
b Sign Test

LEGENDA: VASCONTR: VAS at the follow up
VASINIZI: initial Vas

Figure 5

Table 4

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
KPS2 - KPS1	Negative Ranks	0	,00	,00
	Positive Ranks	19	10,00	190,00
	Ties	2		
	Total	21		

a KPS2 < KPS1
b KPS2 > KPS1
c KPS1 = KPS2

Test Statistics

	KPS2 - KPS1
Z	-3,921
Asymp. Sig. (2-tailed)	,000
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Based on negative ranks.
b Wilcoxon Signed Ranks Test

Sign Test

Frequencies

		N
KPS2 - KPS1	Negative Differences	0
	Positive Differences	19
	Ties	2
	Total	21

a KPS2 < KPS1
b KPS2 > KPS1
c KPS1 = KPS2

Test Statistics

	KPS2 - KPS1
Exact Sig. (2-tailed)	,000

a Binomial distribution used.
b Sign Test

LEGENDA: KPS1: Initial Kranofsky performance status
KPS2: Kranofsky performance status at the end of therapy

Figure 6

Table 5

Wilcoxon Signed Ranks Test

Ranks

		N	Mean Rank	Sum of Ranks
KPS3 - KPS1	Negative Ranks	0	,00	,00
	Positive Ranks	15	8,00	120,00
	Ties	6		
	Total	21		

a KPS3 < KPS1
b KPS3 > KPS1
c KPS1 = KPS3

Test Statistics

	KPS3 - KPS1
Z	-3,502
Asymp. Sig. (2-tailed)	,000
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Based on negative ranks.
b Wilcoxon Signed Ranks Test

Sign Test

Frequencies

		N
KPS3 - KPS1	Negative Differences	0
	Positive Differences	15
	Ties	6
	Total	21

a KPS3 < KPS1
b KPS3 > KPS1
c KPS1 = KPS3

Test Statistics

	KPS3 - KPS1
Exact Sig. (2-tailed)	,000
Exact Sig. (1-tailed)	,000
Point Probability	,000

a Binomial distribution used.
b Sign Test

LEGENDA: KPS1 = Initial Kranofsky performance status
KPS3 = Kranofsky performance status at the follow up

They show a significant decrease of the pain and improvement of the life quality after therapy and in the follow up. Collateral effects were registered in 36% (22%-53%) of the cases: the most common were confusion (n=3), sleepiness (n=3), epigastralgia (n=2), vertigos, arterial hypertension, headache and generalized oedema (n=1 for each type).

CONCLUSIONS

Pregabalin statistically turned out to be effective in peripheral neuropathic not oncological pain treatment, in terms of diminishing pain and in terms of life quality. Two patients haven't had any clinical benefit, while 4 patients had benefit from the treatment but, at the 2 months from the suspension of the drug control, clinical condition was the same as at the beginning of therapy. 42% (24%-62%) of the studied population had clinical benefit at the dosage of 150 mg/die, 24% (11%-45%) at 300 mg/die and 34% (18%-55%) at the maximum dosage of 600 mg/die. Therefore in 68% (47%-84%) of the patients it wasn't necessary to reach the maximum dosage, with consequent better compliance and tolerability. A high percentage of collateral effects was registered (36% (22%-53%) of the population), which induced drug suspension. The most frequent collateral effects were confusion and drowsiness.

CORRESPONDENCE TO

G. B. Venier, E. mail: gbvenier@asl14chioggia.veneto.it tel. 0415534338, Fax 0415534394.

References

1. Portenoy R.K.: Pain management: theory and practice. Neuropathyc pain. Philadelphia FA Davis Company, 1996; 83-125.
2. Galer B.S.: neuropathic pain peripheral origin: advances in pharmacologic treatment. Neurology, 1995; 45 (suppl 9): S 17-S 25.
3. Meyer-Rosberg K., Kvarnstrom A., Kinnman E., Gordh T., Nordfors L-O., Kristofferson A.: Peripheral neuropathic pain: a multidimensional burden for patients. Eur J Pain, 2001; 5: 379-389.
4. Freynhagen R., Strojek K., Griesing T., Whalen Ed., Balkenohl M.: Efficacy of Pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain, 2005; 115: 254-263.
5. Taylor C.P.: The biology and pharmacology of calcium channel alpha2-delta proteins. CNS Drug Rev, 2004; 10(2): 183-188.
6. Ben-Menachem E.: Pregabalin pharmacology and ist relevance to clinical practice. Epilepsia, 2004; 45 (suppl 6): 13-18.
7. Frampton J.E., Scott L.J.: Pregabalin in the treatment of painful diabetic peripheral neuropathy. Drugs, 2004; 64 (24): 2813-2820.
8. Field M.J., Oles R.J., Lewis A.S., McCleary S., Hughes J., Singh L.: Gabapentin and S-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. Br J Pharmacol, 1997; 121: 1513-1522.
9. Paulin L., Giorgi I.; Modelli di valutazione del dolore. UTET, 1999.
10. Dworkin R.H., Corbin A.E., Young J.P., Sharma U., La Moreaux L., Bockbrader H., Garofalo E.A., Poole R.M.: Pregabalin for the treatment of postherpetic neuralgia. A randomized, placebo-controlled trial. Neurology, 2003. 60: 1274-1283.
11. Fink K., Dooley D.J., Meder W.P., Suman-Chauhan N., Duffy S., Clusmann H., Gothert M.: Inhibition of neuronal Ca influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology, 2002; 42: 229-36.
12. Dooley D.J., Donovan C.M., Meder W.P., Whetzel S.Z.: Preferential action of gabapentin and pregabalin at P/Q-type voltage-sensitive calcium channels: inhibition of K-evoked norepinephrine release from rat neocortical slices. Synapse, 2002; 45: 171-90.
13. Maneuf Y.P., Hughes J., McKnight A.T.: Gabapentin inhibits the substance P facilitated K-evoked release of glutamate from rat caudal trigeminal nucleus slices. Pain, 2001; 93: 191-6.

Author Information

A. Cinetto, M.D.
Department of Critical Care, O.U. Anaesthesiology and Critical Care

E. Ferrulli, M.D.
Department of Critical Care, O.U. Anaesthesiology and Critical Care

G. B. Venier, M.D.
Director, Department of Critical Care, O.U. Anaesthesiology and Critical Care