Palestrica of the third millennium – Civilization and Sport
Vol. 16, no. 3, July-September 2015, 214–218

Effects of tramadol treatment on aerobic exercise capacity in subjects with chronic non-specific low back pain
Efectele administrării de tramadol asupra capacității aerobe de efort la subiecți cu lombosacralgie cronică nespecifică

Andreea Marilena Ionescu [1], Bogdan Nicolae Manolescu [2], Roxana Popa [3], Ruxandra Badea [1], Simona Săvulescu [1], Simona Tache [4], Mihai Berteanu [1]

[1] Clinical Rehabilitation Department, Elias Emergency University Hospital, Bucharest
[2] "C. Nenițescu" Department of Organic Chemistry, Faculty of Applied Chemistry and Science of Materials, Politehnica University, Bucharest
[3] IBM Romania, Bucharest
[4] Physiology Department, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca

Abstract

Background. Chronic non-specific low back pain is a common disorder associated with a high degree of physical deconditioning.

Aims. To assess the effect of tramadol administration on pain and aerobic exercise capacity in human subjects with chronic non-specific low back pain.

Methods. The study was conducted from June to December 2015, at the Clinical Rehabilitation Department of the Elias Emergency University Hospital in Bucharest. The study population consisted of 25 subjects suffering from chronic non-specific low back pain. They were divided into a placebo group and a tramadol group. The medication consisted of tramadol (50 mg) capsules, and placebo respectively, disposed as identical capsules. Both tramadol and placebo were administered orally twice a day, for a period of seven days. All subjects completed the visual analogue scale and underwent cardiopulmonary exercise testing using a cycle ergometer with progressively increasing work rate until the exercise was symptom limited at the baseline and at the end of the study. For each subject, pain response, peak oxygen uptake (VO_2 max), aerobic contribution to exercise (VO_2/WR), ventilatory efficiency (VE/VCO_2) were investigated baseline and after 7 days of treatment.

Results. The results of VAS were significantly lower for the tramadol group; in this group, VO_2 max and VO_2/WR significantly increased. The ventilatory efficiency improved, the VE/VCO_2 values significantly decreasing in the tramadol group.

Conclusions. In chronic non-specific low back pain subjects, tramadol reduces pain, improves aerobic exercise capacity and effort tolerance.

Key words: tramadol, deconditioning, low back pain.

Rezumat

Premize. Lombosacralgia cronică nespecifică este o afecțiune comună, asociată cu un grad înalt de decondiționare fizică.

Obiective. Evaluarea efectelor administrării de tramadol asupra durerii capacității aerobe de efort fizic, la subiecți umani cu lombosacralgie cronică nespecifică.

Metode. Studiul s-a desfășurat în perioada iunie-decembrie 2015, la Clinica Recuperare Medicală a Spitalului universitar de Urgență Elias, București. 25 subiecți umani cu lombosacralgie cronică nespecifică au intrat în studiu. Au fost randomizați în 2 loturi: Martor și Tramadol. S-a administrat tramadol capsule 50 mg, respective placebo în aceeași condiționare farmacologică timp de 7 zile. Toți subiecții au completat scala visual analogă de evaluare a durerii și au fost testați la efort cu ajutorul cicloergometrului cu putere progresiv crescândă, la momentul inițial și după 7 zile de tratament. Pentru fiecare subiect s-au urmărit răspunsul la durere, evoluția volumului maxim de oxigen (VO_2 max), contribuției aerobe la efort (VO_2/WR), coeficientului ventilator al dioxidului de carbon (VE/VCO_2) și a frecvenței cardiace, inițial și la sfârșitul celor 7 zile de studiu.

Rezultate. În lotul care a primit tramadol s-a constatat o ameliorare semnificativă statistic a valorilor volumului maxim de oxigen inspirat, a contribuției aerobe la efort, precum și a echivalentului ventilator al dioxidului de carbon. Nu s-au produs modificări în frecvența respiratorie la momentul final al studiului. Analiza statistică de corelație susține efectul tramadolului asupra parametrilor evaluați.

Concluzii. Administrarea de tramadol la subiecții umani cu lombosacralgie cronică nespecifică a redus durerea, a crescut capacitatea aerobă de efort și toleranța la efortul fizic.

Cuvinte cheie: tramadol, decondiționare, lombosacralgie.

Received: 2015, August 3; *Accepted for publication:* 2015, August 30;
Address for correspondence: Bdul Mărăşti 17, Sector 1, Postal Code 011416, Bucharest, Romania
E-mail: andreea2a@yahoo.com
Corresponding author: Andreea Marilena Ionescu, andreea2a@yahoo.com

Introduction

Pain is one of the most important factors in limiting exercise capacity. About 80-85% of back pain episodes have no known aetiology. Low back pain (LBP) is a common problem and a major cause of disability among adults worldwide. It affects over 80% of persons at some point of their life (Harstall & Ospina, 2003). Evidence suggests that for less than 15% of patients with LBP it is possible to assign a specific back pain category, such as trauma, mechanical injury, spinal cord injury, inflammation, infection, and tumours. In the majority of patients, LBP is non-specific (Kool J et al., 2004). Chronic non-specific low back pain (CNSLBP) is pain localized to the lower back without radiation (Manusov, 2012), lasting for more than 12 weeks (Koes et al., 2010).

In time, progressive decrease in physical activity in patients with CNSLBP lowers their aerobic capacity. Deconditioning induces, in turn, even more pain, loss of function and disability in these subjects (Hodlemans et al., 2004; Duque et al., 2009). Tramadol, a centrally acting synthetic analgesic, produces its effect by binding to opioid receptors and by inhibiting reuptake of noradrenaline and serotonin. It is an effective drug for the treatment of moderate to severe pain in a variety of acute and chronic conditions. Tramadol does not have a depressant effect on respiration like most opioids do, and has low abuse potential (Cucuieț et al., 2008). Furthermore, the National Institute for Health and Care Excellence recommended tramadol for people with CNSLBP not responding to other treatment options (1).

Physical exercise is complex stress (neuromuscular, oxidative, respiratory and cardiovascular, endocrine and metabolic, emotional) and a physiological activator of the endogenous opioid system, therefore pain suppression could be considered an adaptive response (Tache & Staicu, 2012).

The effects of tramadol on exercise capacity in human subjects have not been studied. Moreover, there are no other studies regarding the influence of tramadol on exercise capacity in persons suffering from CNSLBP.

Hypothesis

The aim of the present study was to explore the effects of tramadol treatment on pain and aerobic exercise capacity in patients with CNSLBP, and to collect data guiding the design of a larger hypothesis-testing study, based on previous positive experimental observations regarding the effects of chronic tramadol administration on exercise capacity (David et al., 2007), the high prevalence of CNSLBP and WHO recommendations for its management.

Material and methods

Cardiopulmonary exercise testing (CPET) allows simultaneous evaluation of the cardiovascular and respiratory systems performing their major function, that is, gas exchange between cells and the environment. The success of these organ systems in achieving this function is reflected in the O_2 uptake and CO_2 output in response to a specific work rate and their relation to heart rate, ventilation, and to one another. Exercise requires an integrative cardiopulmonary response in order to support the increased respiratory demands (O_2 consumption and CO_2 production) of the muscles in contraction.

Therefore, gas exchange measurements are fundamental in order to understand the causes of exercise limitation (Wasserman et al., 2012).

Research protocol

a) Period and place of the research

The study was conducted in accordance with ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Following the approval of the Ethical Committee of the "Elias" Emergency University Hospital (Bucharest), the informed consent was obtained from all 25 persons enrolled. The study and the measurements were carried out between January and June 2014.

b) Subjects and groups

The patients were recruited one by one during 6 months, in order of their presentation to the Rehabilitation Department of our hospital. Technically, 25 subjects with CNSLBP joined the study. The subjects were randomised into two groups of 12 and 13 patients, by a computer-generated random number. As shown in the flow chart number 1, 35 subjects were enrolled, 10 were excluded (of which 5 did not meet the inclusion criteria, 3 declined to participate, 1 was not compliant to medication, and 1 reported adverse effects – nausea and vomiting).

Group I: Control, 12 subjects, receiving placebo capsules 50 mg orally, twice a day

Group II: Tramadol, 13 subjects, receiving tramadol capsules 50 mg orally, twice a day

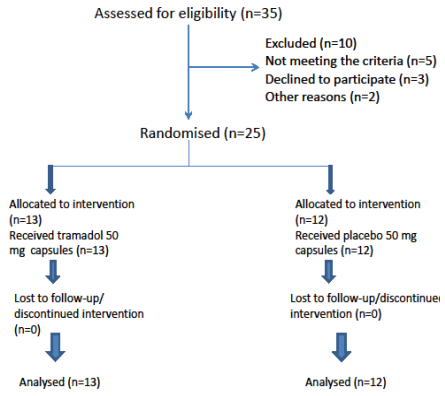

Fig.1 – Flow diagram of progress through the phases of the study (i.e, enrolment, intervention, allocation, follow-up, and data analysis).

The including criterion was the diagnosis of moderate intensity CNSLBP, age 20-60 years. Beyond this, all the subjects were clinically healthy.

Exclusion criteria included known allergy or sensitivity to the drug, obesity, hypertension, cardiac failure, renal insufficiency, diabetes mellitus, viral hepatitis, hepatic cirrhosis, metabolic syndrome, ongoing therapy with sustained-release opioids, MAOI, SSRI, tricyclic antidepressants, neuroleptics, and seizure disorders. Patients who were under treatment with other analgesics, steroidal or non-steroidal anti-inflammatory drugs or

vitamins were also excluded.

c) Tests applied

A single-blinded randomised controlled trial was conducted. The study medication consisted of placebo in group I, and tramadol (50 mg) capsules in group II. Both the placebo and tramadol were given under the same pharmacological conditioning, orally, twice daily for a period of 7 days.

All patients completed the visual analogue scale (VAS) and underwent CPET using a cycle ergometer (Ergoline 100/200, with Cosmed Quark PFT Ergo, produced by Cosmed Italia, Via Pianni de Monte Savello, Rome, Italy), with progressively increasing work rate until the exercise was symptom limited at baseline (T_0) and at the end of the study period (T_1). Practically, the subject exercised on a cycle ergometer while measurements of gas exchange were made, breath by breath, at rest (1 minute), during 2 minutes of low level exercise (warm-up), and while the work rate was increased each minute. The patient was encouraged to continue as long as he/she felt able. To determine the work rate increase, we used the recommended standard procedure.

The following parameters were assessed:

1. VAS - an adapted visual analogue questionnaire, scaled from 1 (no pain) to 6 (worst pain ever)

2. Peak VO_2 (VO_2 max) - highest VO_2 achieved during maximal effort in an increasing work rate exercise test. It is expressed in O_2 milliliters/minute/kilogram. The peak VO_2 is the first measurement to be examined and it establishes whether the patient's physiological responses allow normal maximal aerobic function.

3. Aerobic contribution to exercise (VO_2/WR) - it measures the aerobic work efficiency. The VO_2-work rate relationship describes how much O_2 is utilised by the exercising subject in relation to the quantity of external work performed. It may decrease in cardiovascular diseases.

4. Ventilatory efficiency (VE/VCO_2) - indirect measure of effort tolerance. It measures the efficiency or inefficiency of CO_2 elimination. It has high values in respiratory diseases with ventilation-perfusion mismatching that causes ventilation to be inefficient in eliminating CO_2 from the body (Wasserman et al., 2012).

d) Statistical processing

For data processing, we used StatsDirect v.2.7.2. and Microsoft Office Excel 2007, with comparison statistics as described below.

Results

The two investigated groups were compared. There were no statistical differences between the two groups regarding age and the body mass index.

Subsequently to questionnaire administration (i.e., VAS), data centralisation and processing, the following results, presented in Table I, were obtained: pain was reduced in group I with placebo administration on the last day of study in a statistically non-significant manner. As compared with group II, pain was significantly reduced by tramadol and exercise administration at the end of the study.

The statistical analysis of exercise capacity indicators yielded the following results: peak VO_2 decreased for group I, in a non-significant manner, but it was significantly higher for group II (Table II); aerobic contribution to exercise (VO_2/WR) was smaller for group I, and significantly increased for group II (Table III), ventilatory efficiency (VE/VCO_2) decreased for group I, in a non-significant manner, and it significantly increased for group II (Table IV).

Table I

Comparative analysis of pain indicators studied in the two groups and statistical significance.

Parameter	Group	Time	Mean	SE	Median	SD	Minimum	Maximum		*P*	
VAS	I	T0	3.57	0.137	4	0.514	3	4	T0-T1	T0	0.3550
		T1	2.5	0.139	2.5	0.519	2	3	0.0002	I-II	
	II	T0	3.31	0.151	3	0.602	2	4	T0-T1	T1	< 0.0001
		T1	1.13	0.085	1	0.342	1	2	< 0.0001	I-II	

Table II

Comparative analysis of peak VO_2 studied in the two groups and statistical significance.

Parameter	Group	Time	Mean	SE	Median	SD	Minimum	Maximum		*P*	
VO_2 max	I	T0	21.61	1.225	22.74	4.585	12.8	26.51	T0-T1	T0	0.4475
		T1	20.05	0.983	20.44	3.678	12.8	26.39	0.1465	I-II	
	II	T0	20.75	1.632	18.77	6.528	11.19	33.3	T0-T1	T1	0.1271
		T1	22.92	1.534	22.52	6.136	13.47	36.45	0.0011	I-II	

Table III

Comparative analysis of VO_2/WR studied in the two groups and statistical significance.

Parameter	Group	Time	Mean	SE	Median	SD	Minimum	Maximum		*P*	
VO_2/WR	I	T0	8.21	0.454	8.6	1.7	4.2	10.2	T0-T1	T0	0.0986
		T1	6.67	0.456	6.85	1.706	3.6	9.8	0.0002	I-II	
	II	T0	7.34	0.433	7.75	1.733	4.2	9.8	T0-T1	T1	0.0045
		T1	8.84	0.532	9.35	2.129	5.6	12.7	1.23×10^{-5}	I-II	

Table IV

Comparative analysis of VE/VCO_2 studied in the two groups and statistical significance.

Parameter	Group	Time	Mean	SE	Median	SD	Minimum	Maximum	*P*		
VE/VCO_2	I	T0	26.321	0.719	25.95	2.690	21.7	30.7	T0-T1	T0	0.9939
		T1	26.26	0.673	26.3	2.520	22.3	30.9	0.9447	I-II	
	II	T0	26.33	1.058	25.65	4.232	17.1	35.7	T0-T1	T1	0.1038
		T1	24.21	1.016	23.7	4.065	15.1	32.3	9.68×10^{-5}	I-II	

Discussion

To our knowledge, there are no other clinical studies on the effects of tramadol therapy on exercise capacity in CNSLBP patients.

The aim of this pilot study was to investigate the effect of the administration of 50 mg tramadol on pain and exercise capacity in clinically healthy subjects with CNSLBP.

It was found that tramadol improved all the evaluated parameters. This is also supported by the results of correlation analysis.

Our results are in agreement with experimental studies which have shown that tramadol improves exercise capacity, the psychological state and redox status in trained rats. These findings were explained by the antioxidant and antidepressant effects of this drug (David et. al., 2007; Ionescu & Tache, 2011). As we previously stated, chronic pain is associated with a decrease in exercise capacity, a depressant state (Kool et al., 2004) and mood changes, so the increase in exercise capacity may be a result of the antidepressant action of tramadol.

The analgesic effect of moderate intensity exercise is a well studied issue. Our results are in accordance with these findings (Frontera, 2015). Moreover, tramadol administration reduces pain in human subjects with CNSLBP in the context of physical exercise.

Other studies have shown that tramadol does not have depressant effects on respiration, like most opioids do, suggesting that mechanisms other than opioid receptor activity play a significant role in producing analgesia. Moreover, tramadol was reported to have antitussive effects as shown in a double-blinded randomised, controlled study (Elmawgoud, 2013). In agreement with these findings, our study indicates that tramadol improves VO_2 max and VE/VCO_2 values in patients with CNSLBP.

Pain regulation by the endogenous opioid system and its receptors has been the purpose of many studies starting with 1960. However, documentation is more extensive for those pertaining to the μ-oipioid receptor, as this is the site of action of opiate analgesics (including tramadol) and the receptor most associated with pain suppression (Zubieta, 2009).

Moreover, there are studies demonstrating that the endogenous opioid system may regulate adrenaline and serotonin secretion during physical exercise (Pallazo et al., 2006). Tramadol induces its analgesic effect through two mechanisms. One mechanism relates to a weak affinity for μ-opioid receptors (6000-fold lower compared to morphine). The non-opioid mechanism appears to be related to the ability of tramadol to raise the synaptic levels of the neurotransmitters serotonin and norepinephrine (Raffa & Friederichs, 2003).

Furthermore, serotonin is secreted from the posterior horn in the following conditions: stimulation of the sciatic nerve, inflammatory and chronic pain (Pallazo et al., 2006).

An experimental study has shown that tramadol provides a cardioprotective effect against myocardial ischemia-reperfusion in isolated rat heart (Billir et al., 2007). This is in agreement with our finding that tramadol improved VO_2 max and VO_2/WR (indirect cardiovascular marker) values.

Tramadol, as a weak opioid, is prescribed for any patient suffering from moderate to severe pain including athletes, because the World Anti-Doping Agency (WADA) list available does not include tramadol (2). CNSLBP may disable the individual, decrease exercise capacity and reduce sports performance.

Conclusions

1. Our results indicate that tramadol reduces pain, has a positive effect on aerobic exercise capacity, and improves exercise tolerance when administered to patients suffering from CNSLBP.
2. Taking into account the aforementioned, it could be speculated that tramadol has ergotropic effects and it should be carefully prescribed to athletes because it could be a doping agent. It would be interesting to find out if tramadol would enhance aerobic exercise capacity in athletes too, as a key learning of our study for the design of a future study.
3. Further studies are necessary in order to elucidate the mechanisms by which tramadol improves exercise capacity, as well as to add other clinical applicability to the information obtained.

Conflicts of interest

Nothing to declare.

Acknowledgments

The present article processes data from the doctoral thesis of the first author.

References

Bilir A, Erkasap N, Koken T, Gulec S, Kaygiviz Z, Tanriverdi B, Kurt I. Effects of tramadol on myocardial ischemia-reperfusion injury. Scand Cardiovasc J. 2007;41(4):242-247.

Cucuieț S, Dogaru G, Bild VN, Dogaru T. Modulation of Tramadol antinociception by ketamine and baclofen in mice. Farmacia. 2008; LVI(6):675-693.

David CT, David I, Tache S, Moldovan R. Tramadol influence upon maximal aerobe exercise capacity and upon pain threshold on traine rats. Palestrica of the third Millenium. 2007; 28(2):108-112.

Duque I, Para JH, Duvallet A. Physical deconditioning in chronic low back pain. J Rehabil Med. 2009;41(4):262-266.

Elmawgoud AA. Effect of tramadol on fentanyl induced cough: a double-blind, randomized, controlled study. Egyptian J Anaesthesia. 2013; 29(4): 301-304.

Frontera W. Exercise influencing molecular mechanisms of pain. 9th World Congress of the International Society of Physical and Rehabilitation Medicine. Berlin,19-23 June 2015.

Harstall C, Ospina M. How prevalent is chronic pain? Pain Clinical Updates. 2003;11(2):1-4.

Hodlemans AP, Dijkstra PU, Geertzen JHB, van der Shans CP. Exercise capacity in non-specific chronic low back pain patients: a lean body mass-based Astrand bicycle test; reliability, validity and feasibility. J Occup Rehabil. 2008;18(3):282-289.

Ionescu AM, Tache S. Effects of acute tramadol administration of Tramadol upon effort capacity in rats. Palestrica of the third Millenium. 2011;12(1):11-14.

Koes BW, van Tudler M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the

management of non-specific low back pain in primary care. Eur Spine J. 2010; 19(12):2075-2094.

Kool J, de Bie R, Oesch P, Knüsel O, van den Brandt P, Bachmann S. Exercise reduces sick leave in patients with non-acute non-specific low back pain: a meta-analysis. J Rehabil Med. 2004;36(2):49-62.

Manusov EG. Evaluation and diagnosis of low back pain. Prim Care. 2012;39(3):471-479.

Palazzo E, de Novellis V, Petrosino S, Marabese I, Vita D, Giordano C, Di Marzo V, Mangoni GS, Rossi F, Maione S. Neuropathic pain and the endocannabinoid system in the dorsal raphe: pharmacological treatment and interactions with the serotonergic system. Eur J Neurosci. 2006; 24(7):2011-2020.

Raffa RB, Friederichs E. Profile of Tramadol and Tramadol Analogues. In: Bountra C, Munglani R, Schmidt K, Editors. Pain-Current Understanding, Emerging Therapies, and Novel Approaches to Drug Discovery. Marcel Dekker, New York. 2003,731-742.

Tache S, Staicu LM. Physical effort addaptation of human body. 1st edn. Risoprint Ed. Cluj-Napoca. 2010,143-152.

Wassermann K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, Whipp BJ. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 5th edn. Lippincott Williams&Wilkins Philadelphia; 2012,77-102,141,154-173.

Zubieta JK. Forebrain opiates. In Basbaum AI&Bushnell MC Editors. Science of pain. Elsevier; 2009, 821-827.

Websites

(1) 2015 Prohibited List. Available from: www.wada-ama.org/en/World-Anti-Doping-Program/Sports-and-Anti-Doping-Organizations/International-Standards/Prohibited-List/ Accessed on 2015 March 02.

(2) Low back pain: early management of persistent non-specific low back pain. Published 2009 May. Available at: www.nice.org.uk/guidance/CG88/chapter/key-priorities-for-implementation Accessed on July 2014.