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Research Article

Topiramate in nociceptive pain - experimental analgesia study

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Abstract. Objective: The aim of this study is to assess the action of topiramate on experimental models of nociceptive pain, with acute, subacute and chronic administration within 30 days. Material and methods. We used 50 male Wistar white rats as experimental animals, randomized into 5 groups: a group treated with saline solution, a group treated with metamizole (50 mg/kg), a group treated with tramadol (10 mg/kg), and two groups treated with topiramate (TPM) in different concentrations (10 mg/kg and 50 mg/kg). The following tests have been performed at baseline and after injection (intraperitoneal administration of 0.5 ml/100 g), at specific time points: mechanical paw pressure test, hot plate test and tail-flick test. Results. After a single dose, TPM shows statistically significant antinociceptive effects compared to the values obtained at baseline during various testing times, while performing the hot plate test ($p<0.05$). The use of the paw pressure test and the tail-flick test showed no statistically significant increased pain threshold compared to the values obtained at baseline. Both doses of TPM determine a statistically significant increased pain threshold ($p=0.001$) one hour after administration, compared to the control group and the groups treated with conventional analgesics, and the effect is maintained for up to 24 hours. Increased pain tolerance after TPM administration for 14 days stays high ($p<0.05$) and is obvious in comparison to the control group at all testing times. Antinociceptive profile of TPM after 30 days of administration shows that it increases baseline pain threshold after the first dose, with maximum effect after 14 days, followed by a stable period, without significant increases compared to the baseline. Conclusions. TPM dose of 50 mg/kg has a predominant supraspinal central and prolonged analgesic effect in acute nociceptive pain. TPM dose of 10mg/kg has a predominant spinal analgesic effect (revealed in tail-flick test) and is prolonged in acute nociceptive pain. TPM analgesic effect is superior to the control group and to conventional analgesics tested in acute pain and throughout the entire testing period.

Key Words: analgesia, nociceptive pain, pain threshold, therapeutic efficiency, topiramate.

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Introduction

The complex pharmacodynamic mechanism of topiramate is currently approved for only two major diseases: epilepsy, mono or combined therapy, and preventing episodes of migraine. However, there are many other studies that emphasize other potential clinical effects deriving from its complex action and leading to its use in acute nociceptive pain and neuropathic pain management.

Topiramate inhibits the action potential generated by repeated depolarization of neurons through blockage of sodium channels(Shank *et al* 1994; Perucca 1997) and some voltage-dependent L-type calcium channels, inhibiting calcium current (Shank *et al* 1994; Shank *et al* 2000).

Studies have shown that lower concentrations of topiramate selectively inhibits kainate receptor-mediated synaptic currents containing the GluR5 subunit (GLUK1) and also inhibits, reducing the effectiveness, the postsynaptic transmission of the action potential by blocking the glutamate AMPA receptor (Braga *et al* 2009). Glutamate action on kainate receptors, facilitating transmission of excitatory potential, leads to the inhibition of GABA release, so topiramate inhibition of kainate receptors will favor GABA release and increase GABA(A) receptor-mediated inhibitory current (Braga *et al* 2009; Gryder *et al* 2003). Topiramate inhibits carbonic anhydrase, CA-II and CA-IV isoenzymes, but this mecanism is unlikely to explain its anticonvulsant and antinociceptive action (Wieczorkiewicz-Płaza *et al* 2004). Studies suggest that topiramate can be used to alleviate pain caused by diabetic neuropathy and migraines, in lower doses than those used to treat epilepsy (Spina *et al* 2004; Naegel *et al* 2010).

Its normothymic stabilizing effect also occurs at lower doses than it does with anticonvulsant doses. Therefore, initially used as anticonvulsant, topiramate is currently used by psychiatrists to treat bipolar disorder, anxiety disorders, ADHD and substance abuse (Marcotte 1998; Maidment 2002).

The purpose of this study is to assess the action of topiramate on experimental models of nociceptive pain, with acute, subacute and chronic administration.

Analysis of results aims to assess not only the influence of topiramate on the latency of pain threshold stimulus emergence, but also pain threshold dynamics throughout the testing period. These measurements provide information on the immediate action of topiramate (acute nociceptive pain) and on its action site: peripheral or central, depending on the test used and on the intensity of the antinociceptive action compared to conventional analgesics. Pain threshold dynamics throughout the testing period indicates how repeated administration of topiramate can influence the effectiveness of long-term therapy.

Material and methods

Experimental animals: 50 male Wistar white rats with initial weight between 110-240 g, obtained from "Iuliu Haţieganu" University of Medicine and Pharmacy biobase, Cluj-Napoca. Experimental animals were kept in standard environmental and diet conditions, constant temperature and humidity, and natural light-dark cycle. The animals were randomly divided into five groups of 10 rats each one. The control group was injected intraperitoneally with 0.5 ml/100g saline solution (C). Two groups were injected with conventional analgesics, 50 mg/kg metamizole (M) and 10 mg/kg tramadol (T).

The investigated substance, topiramate, was administered in two different doses: 50 mg/kg (TPM50) and 10 mg/kg (TPM10).

Test methods

Paw pressure test was used in order to measure the analgesic effect using a Ugo Basile Analgesy-Meter (Italy). Paw pressure test is a mechanical analgesic method that measures the threshold response to pain while gradually increasing pressure on the paw, estimating the weight when the rat withdraws its paw.

Hot plate test assesses heat sensitivity of the paw using a Ugo Basile hot plate (Italy) heated to 55°C. The plate was kept at a constant temperature of 55±0.1°C. Hot plate test is a thermoanalgesic method that measures the threshold response to pain of the defense reaction of the paw to the heat stimulus. The animals were each placed on the hot plate and the time of their first reaction to heat was recorded.

During tail-flick test, pain was induced by focusing an infrared light beam on the animal's tail, about 4 cm from the tip of the tail. The reflex response is represented by the interval between light beam projection and tail flick, and is measured electronically. A Ugo Basile Tail-Flick Unit (Italy) was used.

For all three tests, the evaluation was made prior to injection (baseline), 1, 2, 4 hours after acute administration, and 2, 4, 6 hours after subacute and chronic administration.

Statistical analysis was performed using Medcalc 12.5.0.0. The results were statistically processed and expressed as mean and standard deviation. ANOVA for repeated measures was used to test if the average values of the measurements were significantly different between different testing times. Results were considered statistically significant for $p<0.05$. Pearson correlation was subsequently applied to check if there is an association between measurement values determined through various tests and post-hoc tests consisting of pairwise comparisons between the groups of animals studied.

The experimental protocol is in accordance with the Council Directive 86/609/ECC of 24 November 1986 on animal studies and with the Romanian legislative framework.

Results

Threshold response to pain after single-dose administration of research substances in acute nociceptive pain

The group injected with 0.9% NaCl (control group) did not show statistically significant differences between baseline values and those recorded after 1, 2, 4 and 24 hours, for any of the methods used to test pain response.

The group injected with metamizol (50 mg/kg) showed a significant increase in threshold response to pain compared to baseline values, after one hour ($p=0.03$), 2 hours ($p=0.05$) and 4 hours ($p=0.05$), changes recorded only if the measurements were performed using the hot plate.

The group injected with tramadol (10 mg/kg) showed a highly statistically significant increase in pain threshold compared to baseline values, one hour after administration ($p<0.001$), but only for measurements using the hot plate.

The group treated with TPM (50 mg/kg) showed a statistically significant increase in pain threshold for measurements using the hot plate. The increase was observed at all time points compared to the average values of baseline measurements, after one hour and 2 hours ($p=0.001$), 4 hours ($p=0.012$), and 24 hours ($p=0.03$). Pain threshold analysis using tail flick test and the analgesy meter showed no statistically significant increase in pain threshold (Table 1).

Table 1. Pain threshold levels (mean±SD) 1, 2, 4 and 24 hours after administration of 50 mg/kg TPM

TPM 50 mg/kg	Paw pressure test	Hot plate test	Tail-flick test
Baseline (mean±SD)	6.8±0.85	1.09±0.3	2.85±0.76
One hour (mean±SD)	9.02±1.76	5.35±1.86 p=0.001	3.38±0.89
Two hours (mean±SD)	8.2±1.84	5.48±1.91 p=0.001	3±1.39
Four hours (mean±SD)	8±1.85	4.16±1.99 p=0.012	3.45±2.11
Twenty-four hous (mean±SD)	8.42±2.32	4.28±2.57 p=0.03	3.17±1.1

Table 2. Pain threshold levels (AM+/-SD) 1, 2, 4 and 24 hours after administration of 10 mg/kg TPM

TPM 10 mg/kg	Paw pressure test	Hot plate test	Tail-flick test
Baseline (mean±SD)	6.85±0.77	1.09±0.12	2.9±0.55
One hour (mean±SD)	11.6±4.32	4.7±1.54 p=0.001	4.6±1.88
Two hours (mean±SD)	7.77±1.35	3.01±0.96 p=0.001	4.7±1.81
Four hours (mean±SD)	8±1.06	3.04±1.57 p=0.02	3.25±1.4
Twenty-four hours (mean±SD)	10.2±2.25 p=0.008	4±1.88 p=0.009	4±0.94

Table 3. Statistical significance level when comparing the two tested doses of TPM with placebo, metamizole and tramadol in acute administration

		Paw pressure test				Hot plate test				Tail-flick test			
Lot	**Lot**	**1h**	**2h**	**4h**	**24h**	**1h**	**2h**	**4h**	**24h**	**1h**	**2h**	**4h**	**24h**
TPM 50 mg/kg	**C**	ns	ns	ns	ns	0.001	p<0.05	p<0.05	p<0.05	ns	ns	ns	ns
	M	ns	ns	ns	ns	0.001	p<0.001	0.002	p<0.05	ns	ns	ns	ns
	T	ns	ns	ns	ns	0.002	p<0.001	p<0.001	p<0.05	ns	ns	ns	ns
	TPM10	ns	ns	ns	ns	ns	p<0.05		ns	ns	ns	ns	ns
TPM 10 mg/kg	**C**	0.007	ns	ns	0.001	0.001	p<0.05	p<0.05	p<0.05	ns	0.03	ns	ns
	M	ns	ns	ns	ns	0.001	ns	ns	p<0.05	p<0.05	ns	ns	0.01
	T	ns	ns	ns	ns	0.005	ns	ns	p<0.05	ns	ns	ns	ns

Measurements performed for the group treated with 10 mg/kg TPM showed significant increase in pain threshold compared to baseline measurements for paw pressure test after 24 hours (p=0.008), and for hot plate test at all time points: after one hour (p=0.001), 2 hours (p=0.001), 4 hours (p=0.02), and 24 hours (p=0.009). Average tail-flick test measurements were not significantly different from baseline measurements (Table 2).

Analgesic effects of TPM, compared to the control group (C), metamizole (M) and tramadol (T) in acute administration

Pain threshold following administration of 50 mg/kg TPM determined a statistically significant increase compared to the control group and groups treated with metamizole and tramadol, at all time points in hot plate test (Table 3).

Thermoanalgesic test of the group treated with 10 mg/kg TPM revealed an increase in analgesic effect compared to the control group, at all time points (Table 3). Significant increase in pain sensitivity has been reported one hour and 24 hours in mechanical test, and 2 hours in tail-flick test. Compared to conventional analgesics, TPM 10 mg/kg has a more pronounced analgesic effect 1 hour and 24 hours in hot plate test. Compared to metamizole, tenderness differences are also obvious one hour and 24 hours in the tail-flick test.

The comparison between the groups treated with TPM at different doses only shows significant increase in pain threshold 2 hours in the hot plate test (p<0.05) (Table 3).

Pain threshold evolution after administration of investigated substances for 14 days (subacute administration)

Analysis of the group treated with 0,9% NaCl showed no statistically significant differences from baseline in none of the applied tests.

Analysis of the group treated with metamizole for 14 zile showed no statistically significant differences in baseline pain threshold when performing the mechanical and the thermal tests. Tail-flick test showed statistically significant increase 2 hours after the administration of the daily dose.

There have been statistically significant increases in the group treated with tramadol 2 hours after performing the mechanical test. There have been no statistically significant differences for the hot plate test and the tail-flick test.

For the group treated with 50 mg/kg TPM we obtained statistically significant increases in pain threshold 1 hour after in mechanical test. Hot plate test and tail-flick test showed no statistically significant differences (Table 4).

Table nr. 4. Pain threshold levels (AM+/-SD) 2, 4, 6 hours after administration of 50 mg/kg TPM, test perfomed on day 14, compared to baseline levels.

TPM 50mg/kg	**Paw pressure test**	**Hot plate test**	**Tail-flick test**
Baseline (mean±SD)	6.8±1.07	2.49±0.87	3.81±0.9
Two hour (mean±SD)	9.45±1.84 **p=0.01**	2.18±0.54	3.76±1.19
Four hours (mean±SD)	7.55±1.84	2.06±0.77	4.02±1.08
Six hours (mean±SD)	8.95±1.51	2.16±0.95	3.59±0.67

Table 5. Pain threshold levels (AM+/-SD) 2, 4, 6 hours after administration of 10mg/kg TPM, test performed on day 14, compared to baseline levels

TPM 10 mg/kg	**Paw pressure test**	**Hot plate test**	**Tail-flick test**
Baseline (mean±SD)	9.22±2.91	3.46±1.24	4.26±1.23
Two hour (mean±SD)	9.62±0.90	1.84±0.88	4.26±1.37
Four hours (mean±SD)	10±2.16	1.61±0.55	4.30±1.71
Six hours (mean±SD)	8.37±1.63	1.87±0.79	4.16±1.04

Analgesic effects of TPM compared to the control group (C), metamizole (M) and tramadol (T) groups, in subacute administration, depending on the procedure

The group undergoing subacute administration of TPM 50 revealed significantly increased effects compared to the control group at all testing time during the hot plate test. Compared to tramadol, the pain threshold significantly increases from baseline levels (p<0.05) during the same test. TPM 10 significantly increases the pain threshold compared to the control group (baseline, 2 and 6 hours after) and to the groups treated with M and T groups (baseline) in hot plate test (Table 6). Mechanical

test and tail-flick test do not show significant changes for TPM in any of the doses tested.

Table 6. Statistical significance when comparing the two doses of TPM with placebo, metamizol and tramadol, in subacute administration, in hot plate test

		Hot plate test			
Lot	**Lot**	**Baseline**	**2h**	**4h**	**6h**
TPM 50 mg/kg	**P**	p<0.05	p<0.05	p<0.05	p<0.05
	M	ns	ns	ns	ns
	T	p<0.05	ns	ns	ns
	TPM10	ns	ns	ns	ns
TPM 10 mg/kg	**P**	p<0.05	p<0.05	ns	p<0.05
	M	p<0.05	ns	ns	ns
	T	p<0.05	ns	ns	ns

Pain threshold levels after administration of research substances for 30 days (chronic administration)

The analysis of the control group mentioned no statistically significant differences between the mean pain threshold levels for any of the tests performed. Tail-flick test measurements for subjects treated with metamizole showed no statistically significant differences. Mean paw pressure test determined statistically significant increases in pain threshold between baseline and measurements performed after 2 hours (p=0.02) and 6 hours (p=0.002), metamizole acting as a painkiller in short-term acute pain, even after long-term administration. There have been no statistically significant differences in pain threshold in the group treated with tramadol, during the paw pressure test, hot plate test and tail-flick test.

Table 7. Pain threshold levels (AM+/-SD) 2, 4, 6 hours after administration of TPM10 and TPM50, compared to baseline levels, measurements performed on day 30, in the 3 used tests.

TPM 50 mg/kg	**Paw pressure test**	**Hot plate test**	**Tail-flick test**
Baseline (mean±SD)	8.25±1.44	1.41±0.33	4.92±1.05
Two hour (mean±SD)	7.58±1.22	2.67±1.07 **p=0.02**	4.13±1.11
Four hours (mean±SD)	8.36±1.36	1.45±0.57	5.02±1.34
Six hours (mean±SD)	7.56±1.32	1.64±0.21	4.94±1.42
TPM 10 mg/kg	Paw pressure test	Hot plate test	Tail-flick test
Baseline (mean±SD)	7.44±1.15	1.19±0.26	5.12±0.85
Two hour (mean±SD)	8.45±0.84	1.81±0.84	5.09±1.21
Four hours (mean±SD)	8.15±0.76	1.99±1.16	4.33±0.98
Six hours (mean±SD)	7.93±1.06	1.41±0.26	4.83±0.87

Analysis of the groups treated with TPM, compared with baseline values, revealed no statistically significant increases in pain threshold, except from the group treated with 50 mg/kg TPM, 2 hours in hot plate test. Baseline levels were relatively high and thus, pain threshold increases have not been statistically significant even though there were high pain threshold levels (Table 7).

Analgesic effects of TPM compared to placebo (P), metamizole (M) and tramadol (T), in chronic administration, depending on the procedure

Chronic administration of TPM significantly increases baseline pain threshold levels so that there are no relevant increases in pain threshold after administration after the dose is stabilized. A balance dose is assumed to maintain a constant analgesic effect. Compared to the control group, pain threshold changes are obvious only in tail-flick test: baseline, 2, 4, and 6 hours after administration (Table 8).

TPM (50 mg/kg) does not show any significant increase in pain threshold when using the analgesy meter throughout the 30 days of testing (Fig. 1). TPM (10 mg/kg) increases the threshold response to pain mainly after 14 days, with significant pain threshold levels 2 hours (p=0.004) and 4 hours (p=0.01) after administration, as illustrated in Fig. 1.

Pressure test performed on the group treated with TPM (50 mg/kg) shows significant increases in baseline pain threshold levels on day 14 compared to the first testing day (p=0.004) and the last testing day (p=0.03). Baseline levels have increased after the first day of administration and remained high until the last testing day (p=0.008). Paw pressure test for TPM (50 mg/kg) shows elevated levels after the first administration, significantly higher than the values obtained at similar times 14 and 30 days after administration.

TPM (10 mg/kg) is similar to TPM (50mg/kg), recording significant increase in pain threshold level after the first administration, remaining elevated from the first day until the 14th day, then decreasing (Fig. 1).

Tail-flick test performed on the group treated with TPM (50mg/kg) shows increased pain threshold levels after 30 days, statistically significant after 4 hours (p=0.006), compared to the values recorded at similar previous times (Fig. 1). TPM (10mg/kg) has similar behavior, but without significantly elevated levels throughout the 30 days of administration.

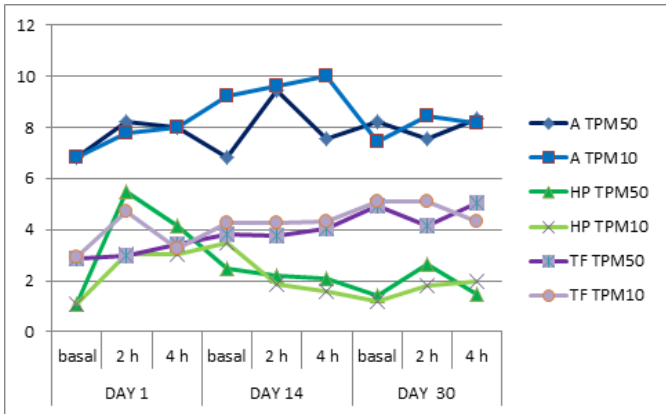

Figure 1. Pain threshold evolution for 30 days for the groups treated with TPM. The ordinate shows the response latency according to procedure, the abscissa shows pain threshold evolution during the chosen testing times.

Table 8. Statistical significance of TPM in comparison with the control group (C) and conventional analgesics inthe tail-flick, 30 days after administration.

Lot	Tail-flick test											
	Baseline			2 h			4 h			6 h		
	C	M	T	C	M	T	C	M	T	C	M	T
TPM 50 mg/kg	p<0.05	ns	ns	ns	ns	ns	p<0.05	ns	ns	p<0.05	ns	ns
TPM 10 mg/kg	p<0.05	ns	ns	p<0.05	ns	ns	p<0.05	ns	ns	p<0.05	ns	ns

Discussions

Analysis of the groups treated with a single dose of TPM reveals obvious antinociceptive effects with statistically significant increase in pain threshold at all time points when performing the hot plate test (p<0,05).

The results obtained in the first hours after administration are highly statistically significant (p=0.001) for both doses of TPM compared to baseline values.

The mechanical test and the tail-flick test showed no statistically significant changes in pain threshold which attests TPM's central action.

Antinociceptive effect of both doses of TPM is rapid, with highly significant increase (p=0.001) one hour in the pressure test, compared to the control group and the groups treated with conventional analgesics. Maintenance of effect is obvious the mentioned test and remains significantly increased up to 24 hours compared to the control group and the groups treated with tramadol and metamizole. The long half-life of TPM is highlighted by increased pain threshold 24 hours after the first administration (p=0.008), compared to baseline levels.

There have been few studies on TPM effect in somatic nociceptive pain, one study indicating antinociceptive effects after intraperitoneal administration of 50 mg/kg and 100 mg/kg using hot plate test (Paudel *et al* 2011). However, results obtained for acute visceral pain indicate that at a dose of 10 mg/kg (same dose as the one we used) TPM has significant antinociceptive effect (Stepanovic-Petrovic *et al* 2008). The same study shows that the antinociceptive effect observed in TPM and GBP (gabapentin) occurs at doses which do not display significant adverse effects(Stepanovic-Petrovic *et al* 2008). Most preclinical studies indicate that TPM has antinociceptive effect in neuropathic pain(Wieczorkiewicz-Płaza *et al* 2004; Benoliel *et al* 2006), induced by various models of neuropathic pain but at doses of 20-50 mg/kg. Efficiency at low doses observed in this study is consistent with other studies suggesting that low doses of TPM (10-20 mg/kg) are also effective in neuropathic pain (Benoliel *et al* 2006), side effects being dose dependent.

TPM has a complex mechanism of action involving inhibition of sodium and calcium channels, increasing the activity of chloride channels in neurons or glial cells, thus reducing the excitability of neuronal circuits (Shank *et al* 2008). These mechanisms are added by selective inhibition, in relatively low concentrations, of synaptic currents mediated by AMPA/kainate receptor-mediated glutamate (Gryder *et al* 2003;Braga *et al* 2009), and inhibition of carbonic anhydrase (CA-II, CA-IV isoenzymes)(Shank *et al* 1994; Dodgson *et al* 2000). Some studies suggest modulation of potassium channels (Herrero *et al* 2002; Russo *et al* 2004) and action on certain proteins involved in neurotransmitter release from synaptic terminals (Okada *et al* 2005a). Despite these multiple pharmacodynamic properties of TPM, there is a common molecular mechanism suggesting that TPM can prevent ATP phosphorylation and its binding to certain receptors, ion channels or auxiliary proteins blocks their activation (Shank *et al* 2000; Angehagen *et al* 2004).

There are many other studies suggesting other potential clinical effects resulting from its complex action that can at least partly explain the action it has at low doses in acute nociceptive pain, as observed in our study.

It is important to remember that following nociceptive excitation, glutamate acts mainly on AMPA receptors causing brief excitation only when the stimulus is increased or if there is repeated stimulus release, NMDA receptor activation or tachykinin NK1 and NK2-receptor activation in inflammatory processes (Petrenko *et al* 2003; Mc Roberts *et al* 2001).

TPM blocks AMPA/kainate receptors, reducing the excitability induced by glutamate action (Braga *et al* 2009). TPM has a direct effect on neurotansmitter release, as shown in the studies conducted by Schiffer in 2001, showing that intraperitoneal administration of TPM at a dose of 25-50 mg/kg determines a 50-70% decrease in nicotine-induced dopamine release in rats (Schiffer *et al* 2001; Shank *et al* 2008). Similar studies have shown that TPM acts on the release of monoamine in the prefrontal cortex in rats after release induction by means of various procedures (Okada *et al* 2005a; Okada *et al* 2005b). These results suggest that TPM has a direct effect on the activity of certain proteins involved in exocytosis (Shank *et al* 2008) and, therefore, on the release of excitatory neurotransmitters.

The pharmacological effects of TPM seem to be related to the interaction with protein subunits in various ion channels or receptors, which in turn are activated by phosphorylation(Shank *et al* 2008). It was observed that the effect of TPM on the activity of these proteins can be immediate, delayed or gradual (Angehagen *et al* 2004). The results obtained in several studies support the idea that TPM acts directly by binding to the site of protein phosphorylation activation, preventing gaining ATP access to this binding site and prolonging protein dephosphorylation, or indirectly by inhibiting certain protein kinases (c-AMP protein kinase, protein kinase C, calmodulin) or activating certain phosphatases, such as calcineurin (Shank *et al* 2000; Angehagen *et al* 2004). If binding to this action site only occurs when these proteins are dephosphorylated, then this could be a possible explanation for the immediate or delayed action of TPM (Shank *et al* 2000; Angehagen *et al* 2004; Shank *et al* 2008).

TPM effect after repeated administration (14 days) using the paw pressure test is obvious through elevated baseline levels compared to the control group and the groups treated with

conventional analgesics. Increased threshold response to pain after TPM administration remains elevated ($p<0.05$) and obvious in comparison to the control group, at all time points. These clues are important for long-term therapy effectiveness and are reflected in clinical trials showing TPM efficacy in preventing therapy of migraine attack (Ruiz *et al* 2009; Naegel *et al* 2010), in neuropathic pain therapy (Wieczorkiewicz-Płaza *et al* 2004), and in the treatment of mental illnesses (Marcotte *et al* 1998; Maidment 2002).

The antinociceptive effect of TPM, 30 days after administration, shows that it increases the baseline pain threshold after the first dose, with maximum effect after 14 days, followed by a stable level, without significant increases compared to baseline levels. This process can be compared with dose titration until the medication has achieved the desired therapeutic effect, and reflects predictable linear kinetics, also encountered in clinical trials. Even if this study is based on a pharmacological approach and mainly investigates TPM action at certain doses and during a certain time interval, it also provides information regarding pharmacokinetics: long-term action, single-dose administration, long-term administration effectiveness.

Conclusions

TPM at a dose of 50 mg/kg has predominant central supraspinal analgesic effect in acute nociceptive pain and for long-term administration. TPM at a dose of 10 mg/kg has predominant spinal analgesic effect (obvious by tail-flick test values) in acute nociceptive pain and for long-term administration. The analgesic effect of TPM is superior to the control group and to conventional analgesics tested in acute pain and throughout the entire testing period.

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