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Effects of repeated tramadol and morphine administration on psychomotor and cognitive performance in opioid-dependent volunteers

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Abstract

Tramadol is an atypical, mixed mechanism analgesic used to treat moderate to severe pain. Based on evidence that tramadol has relatively low abuse potential and can relieve opioid withdrawal, tramadol may be useful for treating opioid dependence. The purpose of this study was to assess the performance side-effect profile of tramadol. Nine opioid-dependent volunteers completed a performance battery following 5–7 days of subcutaneous morphine (15 mg, 4 times/day) and two doses of oral tramadol (50, 200 mg, 4 times/day) in a within subject cross-over design. Morphine was always the first condition, and the order of the two tramadol doses was randomized and double blind. Performance was significantly worse in the morphine condition relative to one or both tramadol doses on measures of psychomotor speed/coordination (circular lights task), psychomotor speed/pattern recognition (DSST speed measure) and psychomotor speed/set shifting (trail-making tasks). There were no significant differences among conditions in DSST accuracy, simple reaction time, divided attention, working memory, episodic memory, metamemory, or time estimation. Neither tramadol dose was associated with worse performance than morphine on any measure. Although practice sessions were conducted prior to the first session to reduce order effects, the possibility that residual practice effects contributed to the differences between tramadol and morphine cannot be ruled out. The high tramadol dose produced worse performance than the low dose only on the balance measure. These findings suggest that tramadol is generally a safe medication with respect to cognitive and psychomotor measures and support tramadol's further evaluation as an opioid dependence treatment.

Keywords

tramadol; morphine; opioid; dependence; performance; cognitive

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1. Introduction

Tramadol is an analgesic medication for the treatment of moderate to severe pain; its analgesic effects are mediated by a combination of mu-opioid agonist effects and norepinephrine and serotonin reuptake inhibition (Kayser et al., 1992; Raffa et al., 1992; Driessen et al., 1993; Desmeules et al., 1996). In its parent form, tramadol exists as a racemic mixture of two active enantiomers that undergo hepatic biotransformation to form N- and O-demethylated compounds (Raffa et al., 1993). The O-demethylated metabolite, (+)-O-demethyltramadol (M1), has considerably greater affinity for the mu-opioid receptor than the parent compound, and is primarily responsible for tramadol's mu-opioid activity. However, this activity is relatively weak in comparison to full mu-agonists (Gillen et al., 2000; Raffa 2008). For example, M1 has been shown to possess one-tenth the affinity for the mu-receptor as morphine (Frink et al., 1996; Gillen et al., 2000), and in humans parenteral tramadol is approximately one-tenth as potent as parenteral morphine in producing analgesia (Gutstein and Akil, 2001), and one-twentieth as potent as parenteral morphine in producing prototypic subjective opioid agonist effects (Epstein et al., 2006; Preston et al., 1991).

Results of several preclinical (Friedrichs et al., 1978; Murano et al., 1978; Yanagita, 1978) and clinical laboratory studies (Barth et al., 1987; Cami et al., 1994; Jasinski et al., 1993; Preston and Jasinski, 1989; Preston et al., 1991) suggest that tramadol has low abuse liability. This conclusion is supported by the fact that tramadol has been widely prescribed for over 40 years in many countries with minimal evidence of diversion and abuse. Several retrospective reports and controlled laboratory studies indicate that tramadol may be effective in relieving opioid withdrawal symptoms (Salehi et al., 2005; Sobey et al., 2003; Tamaskar et al., 2003; Threlkeld et al., 2006; Carroll et al., 2006; Lofwall et al., 2007). The combination of low abuse potential and the ability to suppress withdrawal may make tramadol a useful medication for treating opioid dependence.

Full opioid agonists (e.g., morphine) have been shown to impair some aspects of psychomotor and cognitive performance in some studies (cf. Zacny, 1995 for a review). Few studies have examined the effects of tramadol on performance. Zacny (2005) reported that neither tramadol (50, 100 mg orally) nor morphine (25 mg orally) impaired psychomotor performance relative to placebo in sporadic drug users. Two studies from our laboratory (Carroll et al., 2006; Lofwall et al., 2007) revealed that acute tramadol administration (50–400 mg orally administered) did not impair performance in opioid-dependent volunteers; however, interpretation is complicated because participants were tested while in opioid withdrawal in those studies. The purpose of the present study was to assess the psychomotor/cognitive performance side-effect profile of tramadol by examining the effects of repeated oral tramadol administration (5–7 days) at therapeutic (200 mg/day) and supra-therapeutic (800 mg/day) dose levels relative to the full mu-opioid agonist morphine (60 mg/day subcutaneously for 5–7 days) in opioid dependent volunteers.

2. Methods

2.1 Participants

Participants were nine healthy non-treatment seeking adult community volunteers (7 male, 7 Caucasian/2 African American), with a diagnosis of current opioid dependence (based on DSM-IV criteria; First et al., 1995) and eligibility for (but not enrollment in) opioid agonist treatment. Participant recruiting and screening procedures were similar to those described in detail previously (Strain et al., 2000). Participants ranged in age from 26 to 41 years (mean = 36) and in years of education from 10 to 14 (mean = 12). They reported using opioids a mean of 28.9 ± 0.7 out of the 30 days prior to study enrollment, and spending an average of US \$18.9

± 4.5 per day on heroin. The study was approved by the Institutional Review Board. Participants gave written informed consent and were paid for their participation.

2.2. Procedures

This study was conducted as part of a larger study of tramadol that will be reported elsewhere. Participants resided on a closed 14-bed residential unit for the duration of the study. Participants completed the performance testing battery (see below) following 5–7 days of daily administration of each of three drug conditions in a within subject cross-over design: morphine 15 mg subcutaneously 4 times/day (q.i.d.), tramadol 50 mg orally q.i.d., and tramadol 200 mg orally q.i.d.. Morphine was always the first condition, and the order of the two tramadol doses was randomized and double blind. Participants were informed that during the study they would first be maintained on morphine and then tramadol, and that their morphine and tramadol doses might change. Performance testing was conducted two hours after the second daily dose. Two practice sessions were conducted prior to the first experimental session to reduce order effects. During these practice sessions, each task was performed at least once and most tasks were performed multiple times to minimize practice effects during the experimental sessions.

The performance testing battery included a simple balance task, the circular lights task (a manual device that measures psychomotor speed and coordination; Mintzer et al., 1997), a computerized version of the digit symbol substitution test (DSST; McLeod et al., 1982) (a measure of psychomotor speed/pattern recognition), two computerized trail-making tests (Mintzer et al., 1997) analogous to Part A and Part B of the paper/pencil Trail-Making Test of the Halstead-Reitan Neuropsychological Test Battery (Halstead, 1947; Reitan, 1955) (measures of psychomotor speed and set shifting/conceptual flexibility), a simple reaction time (RT) task (in which single asterisks appeared on the screen at random intervals, and participants clicked on the mouse as soon as they detected each asterisk), and a time estimation task that assessed the participant's ability to accurately estimate the duration of 5-second, 20-second, and 80-second time intervals (Mintzer et al., 1997) (a measure of time perception). A divided attention task was included that assessed the participant's ability to simultaneously perform central visual tracking and peripheral digit monitoring sub-tasks (Kleykamp et al., 2009). Three measures of short-term/ working memory and focused attention were included: a digit recall task that assessed the participant's ability to recall 8-digit strings following short delays (Mintzer et al., 1997), the 'n-back' task that assessed the participant's ability to recall letters presented n-positions back in a continuous string of letters (i.e., 1, 2, or 3 positions back; 0-back was a non-memory control condition in which participants were simply required to respond to a specified target letter in the continuous string) (Jonides et al., 1997; Mintzer and Stitzer, 2002), and a modified Sternberg task that assessed the participant's ability to recall 5-letter strings following short delays (Mintzer et al., 2005). The battery also included a word memory paradigm (Mintzer and Stitzer, 2002) that assessed the participant's ability to recognize (recognition memory) and recall (free recall) a list of words presented in a study list at the beginning of the testing session, following an 80-minute delay (measures of long-term/ episodic memory). The word memory paradigm also assessed participants' confidence in their recognition memory responses (a measure of metamemory: awareness and knowledge of one's own memory). The entire battery took approximately 90 min to complete. These tasks have been described in detail previously (see references cited above) and were administered by a staff member on a Macintosh computer in a quiet session room outside the residential unit.

3. Results

Data from the performance testing battery were analyzed by repeated measures analyses of variance (ANOVAs) with drug condition (morphine 15 mg q.i.d., tramadol 50 mg q.i.d., tramadol 200 mg q.i.d.) and other task-specific variables as factors. Significant main effects

and interactions were followed up with simple effects tests as appropriate and modified Bonferroni corrections were used (cf. Keppel, 1991). Modified Bonferroni-corrected p-values are reported, with $p \leq .05$ considered statistically significant; this is equivalent to $p \leq .033$ uncorrected. Data from one participant were excluded from the analyses on gamma correlations (used to measure metamemory in the word memory paradigm; Goodman and Kruskal, 1954) due to insufficiently distributed data. All other analyses included data from all participants.

On several tasks that assessed aspects of psychomotor performance, performance was significantly worse in the morphine condition relative to one or both tramadol conditions (see Table 1). Specifically, the number of correct responses on the circular lights task and the number of trials completed on the DSST were significantly lower in the morphine condition relative to both tramadol doses. On the trail-making tests, total running time was significantly higher (i.e., slower) in the morphine condition relative to both tramadol doses for trail-making B, and relative to the higher tramadol dose for trail-making A. The difference between the total running time for trail-making B and the total running time for trail-making A (which provides a measure of set-shifting time, controlling for psychomotor speed) was also significantly higher (i.e., slower) in the morphine condition relative to both tramadol doses. There was a dose effect of tramadol such that the number of seconds balanced (simple balance task) was significantly higher for the low relative to the high dose tramadol condition. There were no other significant effects of drug condition, nor interactions between drug condition and any task-specific factors.

In addition to the effects of drug condition described above, the following patterns of effects are of interest because they replicate the results of previous cognitive studies, providing evidence for the sensitivity of these tasks as implemented in the present study. In the n-back task, there was a significant main effect of 'n' on performance, such that performance worsened as a function of 'n' (memory load); this effect was reflected both in a decrease in d' (signal detection measure of the participant's sensitivity in distinguishing between target and non-target stimuli; Snodgrass and Corwin, 1988) and an increase in reaction time as memory load increased. Likewise, in the Sternberg task, there was a main effect of condition such that performance was significantly worse in the delay condition (in which there was a 12-sec delay between presentation of the letter strings and memory testing) relative to the control condition (in which the letter strings remained on the screen during memory testing) as reflected both in a decrease in proportion correct and an increase in reaction time.

4. Discussion

To our knowledge, this is the first study to examine the effects of repeated tramadol administration on cognitive performance in opioid-dependent volunteers. Performance was significantly worse in the morphine condition relative to one or both tramadol conditions on measures of psychomotor speed/coordination (circular lights task), psychomotor speed/pattern recognition (DSST speed measure: number of trials completed) and psychomotor speed/set shifting (trail-making A and B tasks). There were no significant differences among conditions in DSST accuracy (proportion correct), simple reaction time, divided attention, working memory, episodic memory, metamemory, or time estimation. Neither dose of tramadol was associated with worse performance than morphine on any measure.

Although to our knowledge no studies have examined the effects of repeated morphine administration specifically on cognitive performance in opioid-dependent volunteers, several studies have tested acute cognitive effects of a single dose of morphine in healthy volunteers or non-dependent abusers or patients. Consistent with the suggestion of impaired psychomotor speed in the morphine condition in the present study (i.e., fewer correct responses on the circular lights task; fewer trials completed on the DSST; longer running time on trail-making A and B tasks), some of these studies have shown that acute administration of morphine slows

psychomotor speed (e.g., on the DSST and finger tapping tasks; Bruera et al., 1989; Forrest et al., 1977; Zacny, Hill, Black, and Sadeghi, 1998; Zacny, Lichtor, Flemming et al., 1994) and reaction time (e.g., on an auditory RT task; Wikler et al., 1965; Zacny, Lichtor, Flemming et al., 1994). However, it should be noted that other studies in healthy volunteers have found no effect of acute morphine at similar doses on psychomotor or cognitive performance (Hill and Zacny, 2000; Zacny, Conley, and Marks, 1997; Zacny, Lichtor, Thapar et al., 1994). With respect to the current study, the conclusion of impairment in the morphine condition is limited by the absence of a control group or placebo condition. It is also important to note that conclusions regarding differences between tramadol and morphine are significantly limited by the absence of full randomization of drug order; morphine was always the first condition, and only the order of the two tramadol doses was randomized. Although two practice sessions were conducted prior to the first experimental session to reduce order effects, we cannot rule out the possibility that residual practice effects contributed to the observed differences between tramadol and morphine.

Given that the order of the two tramadol doses was randomized, conclusions regarding tramadol dose effects are not limited by order effects. The only measure on which the high tramadol dose produced worse performance than the low dose was balance. The absence of dose-related impairment on most measures despite a 4-fold increase in dose is particularly striking given that the high tramadol dose was four times the typical daily analgesic dose. These findings suggest that tramadol is generally a safe medication with respect to cognitive and psychomotor measures and support tramadol's further evaluation as an opioid dependence treatment.

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Table 1

Mean scores and standard error of the mean (SEM) on experimental measures

Task	Measure	Drug condition					
		Morphine 15 mg q.i.d.		Tramadol 50 mg q.i.d.		Tramadol 200 mg q.i.d.	
		Mean	SEM	Mean	SEM	Mean	SEM
Balance	# seconds balanced	32.33	(7.02)	42.67 [†]	(7.04)	28.67	(7.27)
Circular lights	# correct responses	66.78	(3.97)	79.11 [*]	(4.86)	83.11 [*]	(5.61)
DSST	proportion correct	0.95	(0.02)	0.99	(0.01)	0.98	(0.01)
DSST	# trials completed	39.00	(3.34)	45.78 [*]	(2.79)	45.67 [*]	(3.27)
Trail-making A	running time (sec)	39.18	(5.00)	32.81	(4.56)	31.49 [*]	(3.99)
Trail-making B	running time (sec)	58.80	(10.03)	38.60 [*]	(5.95)	37.47 [*]	(6.27)
Trail-making B-A	running time difference (sec)	19.62	(6.97)	5.79 [*]	(2.96)	5.98 [*]	(2.96)
Simple RT	median RT (msec)	283	(11)	287	(15)	296	(19)
Time estimation	estimate (sec) - 5 sec	5.49	(0.34)	5.10	(0.26)	5.01	(0.23)
Time estimation	estimate (sec) - 20 sec	19.57	(0.99)	19.51	(0.92)	21.88	(0.57)
Time estimation	estimate (sec) - 80 sec	79.86	(3.03)	76.95	(2.20)	63.33	(12.01)
Divided attention	accuracy-central	66.84	(5.07)	71.48	(3.94)	70.98	(3.52)
Divided attention	accuracy-peripheral	93.06	(1.39)	92.59	(1.67)	91.20	(2.64)
Digit recall	number correct	5.22	(1.44)	6.56	(1.11)	7.56	(0.71)
n-back	d' (sensitivity) - 0 back	4.23	(0.00)	4.17	(0.06)	3.87	(0.31)
n-back	d' (sensitivity) - 1 back	3.81	(0.18)	3.63	(0.33)	3.67	(0.20)
n-back	d' (sensitivity) - 2 back	2.78	(0.33)	3.26	(0.34)	2.75	(0.39)
n-back	d' (sensitivity) - 3 back	1.97	(0.35)	2.07	(0.28)	2.41	(0.33)
n-back	median RT (msec) - 0 back	710	(51)	680	(43)	707	(60)
n-back	median RT (msec) - 1 back	766	(66)	754	(54)	795	(66)
n-back	median RT (msec) - 2 back	1026	(103)	913	(83)	915	(115)
n-back	median RT (msec) - 3 back	996	(93)	945	(92)	945	(77)
Sternberg	percent correct-control	97.22	(1.39)	95.37	(2.02)	95.37	(2.02)
Sternberg	percent correct-delay	75.00	(5.73)	79.63	(4.42)	77.78	(6.21)

Task	Measure	Drug condition					
		Morphine		Tramadol		Tramadol	
		15 mg q.i.d.	50 mg q.i.d.	50 mg q.i.d.	200 mg q.i.d.	200 mg q.i.d.	200 mg q.i.d.
		Mean	SEM	Mean	SEM	Mean	SEM
Sternberg	median RT (msec)-control	2360	(191)	2181	(134)	2401	(132)
Sternberg	median RT (msec) -delay	2918	(220)	2849	(226)	2614	(170)
Recognition mem	d' (sensitivity)	1.55	(0.39)	1.18	(0.23)	0.96	(0.41)
Recognition mem	C (response bias)	0.26	(0.18)	0.12	(0.17)	0.16	(0.14)
Recognition mem	gamma (metamemory) [†]	0.25	(0.23)	0.44	(0.12)	0.44	(0.20)
Free recall	# correct responses	5.44	(1.32)	5.67	(1.28)	4.67	(0.87)

DSST = Digit Symbol Substitution Test; RT = Reaction Time; mem = memory

d' = signal detection measure of the participant's sensitivity in distinguishing between target and non-target stimuli

[†] N = 8

* indicates a significant difference relative to morphine ($p \leq 0.05$)

[†] indicates a significant difference relative to high dose tramadol ($p \leq 0.05$)