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Miotic and Subject-Rated Effects of Therapeutic Doses of Tapentadol, Tramadol and Hydromorphone in Occasional Opioid Users

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Abstract

Rationale—Tapentadol is a novel analgesic that activates mu opioid receptors and blocks norepinephrine reuptake. There is very little information available regarding the non-analgesic pharmacodynamic effects of tapentadol.

Objectives—This outpatient study evaluated the physiological, subject-rated and performance effects of therapeutic doses of tapentadol compared to two control drugs in humans.

Methods—This double-blind, within-subject study examined the effects of oral placebo, tapentadol (25, 50 and 75 mg), tramadol (50, 100 and 150 mg) and hydromorphone (2, 4 and 6 mg). Nine occasional opioid users completed the study. Pharmacodynamic drug effects were measured before and for 6 hr after drug administration.

Results—All three doses of the tested drugs produced comparable, time-dependent decreases in pupil diameter, but the effects were generally not dose-dependent. The high dose of tapentadol, as well as all three doses of tramadol and hydromorphone, increased positive subject-rated effects (e.g., “Good Effects,” “Like the Drug”) as a function of time. Only tramadol increased negative subject-rated effects (e.g., “Bad Effects,” “Nauseous”), however these were of low magnitude.

Conclusions—The highest tested dose of tapentadol produced a profile of positive effects comparable to that of hydromorphone, whereas tramadol produced positive and negative subject-rated effects. The mixed findings for tramadol are consistent with previous findings indicating that it has a distinct profile of effects relative to prototypic opioids. Future research should examine the effects of higher tapentadol doses, as well as the factors contributing to the different subject-rated profile of effects observed for tramadol relative to tapentadol and hydromorphone.

Keywords

Subject ratings; miosis; opioid; tapentadol; tramadol; hydromorphone

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Introduction

Tapentadol (Nucynta®) is a novel atypical analgesic that produces its effects through mu opioid receptor activation and norepinephrine reuptake inhibition (Schröder et al., 2010; Tzschentke et al., 2007). Given that tapentadol has both mu opioid and monoaminergic mechanisms of action, it has been compared to another atypical analgesic, tramadol, but the two drugs appear to have important differences that impact their pharmacologic efficacy (Raffa et al., 2012). For example, unlike tramadol, tapentadol does not require metabolism to activate mu opioid receptors (Raffa et al., 2012). Moreover, tapentadol has higher affinity for mu opioid receptors than tramadol (Raffa et al., 2012) and only blocks reuptake of norepinephrine rather than both norepinephrine and serotonin (Tzschentke et al., 2007; 2012). Both tapentadol and tramadol have been approved by the United States Food and Drug Administration for treating moderate to severe pain (Nossaman et al., 2010).

Although there are preclinical and clinical data regarding the analgesic efficacy of tapentadol (Riemsma et al., 2011; Tzschentke et al., 2007), data regarding the non-analgesic pharmacodynamic effects of tapentadol in humans or non-human animals are scant. One technical report shows that tapentadol produces miotic and subject-rated effects similar to those of hydromorphone, but the level of detail available in that report is limited (Australian Therapeutic Goods Administration [TGA], 2011). The purpose of this experiment was to determine the non-analgesic pharmacodynamic effects of therapeutic tapentadol doses compared with two control drugs, tramadol and hydromorphone, in a population of occasional opioid users. We hypothesized that all three drugs would produce comparable prototypic mu opioid effects (e.g., miosis, increased ratings of “Like the Drug”), but that tramadol also would produce negative effects (e.g., increased ratings of “Bad Effects”) based on previous findings (Babalonis et al., 2012; Lofwall et al., 2007; Stoops et al., 2012).

Methods

Subjects

Adult human subjects who reported recreational opioid use in the past year were enrolled in the protocol and were compensated for participation. Subject demographics are described in the Results section. No subject was physically dependent on any drug requiring detoxification and all were in good health verified by medical history, an electrocardiogram and laboratory tests. Individuals seeking treatment for substance abuse or successfully sustaining abstinence were excluded. Persons with past or current history of medical or psychiatric illness that in the opinion of the study physician would interfere with study participation also were excluded. The University of Kentucky Institutional Review Board approved the study and subjects gave sober, written consent prior to enrollment. The consent document stated that oral placebo, tapentadol, tramadol and hydromorphone would be administered. The study was conducted in accordance with the Helsinki guidelines.

Drugs

All drugs were administered in random order, with the exception that a lower dose of each drug had to be administered prior to the high dose and that the high doses of tramadol and hydromorphone had to be administered prior to the high dose of tapentadol as requested by the University of Kentucky IRB. The latter dosing requirement was in place for all subjects except one, who received the high tapentadol dose before receiving the high hydromorphone dose due to experimenter oversight in preparing the dose orders; the University of Kentucky IRB approved this protocol deviation. Immediate-release formulations of tapentadol (25, 50 and 75 mg; Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ), tramadol (50, 100 and 150 mg; UDL Labs, Rockford, IL) and hydromorphone (2, 4 and 6 mg; Halo Pharmaceuticals,

Whippany, NJ) were prepared by over-encapsulating drug with cornstarch filler in opaque gelatin capsules. Placebo capsules contained only cornstarch. The 3-fold range of doses was selected based on data from previous human laboratory studies with tramadol and hydromorphone (Lile et al., 2009; 2010; Zacny, 2005) and to include doses in the therapeutic range (e.g., Afilalo et al., 2010; Beaulieu et al., 2007; Frampton, 2010; Grosset et al., 2005). At the time the study was designed, there were no published human laboratory data on the non-analgesic pharmacodynamic effects of tapentadol, so all of the doses selected were in the therapeutic range for safety, whereas for tramadol and hydromorphone, the two lower doses are in the therapeutic range and the high dose is supra-therapeutic, but within the maximum daily dose range.

Study design

A double-blind, within-subject, placebo-controlled design was used. Ten sessions were conducted on an outpatient basis at the University of Kentucky Laboratory of Human Behavioral Pharmacology (LHBP) during which subjects received one of ten possible dose conditions (i.e., placebo, 25, 50 or 75 mg tapentadol, 50, 100 or 150 mg tramadol, 2, 4 or 6 mg hydromorphone). Prior to completing experimental sessions, subjects completed one practice session, which was used to familiarize subjects with the daily routine and followed the timeline of experimental sessions, with the exception that no medications were administered. Sessions were conducted at least 48 hr apart.

Upon arrival for each session, subjects completed a standard field sobriety test and provided urine specimens and breath samples that were tested for illicit drugs and alcohol to ensure the absence of unauthorized substance use. Five sessions were canceled and rescheduled due to subjects testing positive for outside drug or alcohol use. Females were tested for pregnancy prior to each session; all tests were negative throughout the study. Subjects were instructed to abstain from drinking alcohol for 12 hr prior to a session and from eating or drinking anything for 4 hr prior to session. Subjects were fed a standard, low-fat breakfast upon arrival at the LHBP. After completing sobriety testing and eating breakfast, baseline data were then collected, approximately 30 min before dosing. Doses were administered approximately 1 hr after subjects arrived and experimental measures were completed at hourly intervals for 6 hr after drug administration. Approximately 3 hr after dosing, subjects were allowed to eat lunch and those who reported daily cigarette use were permitted to smoke one cigarette under staff observation. All measures described below were collected prior to and after dosing, with the exception of Street Value, which was only assessed at hourly intervals after dosing.

Experimental measures

Physiological measures—Pupil diameter was determined with a pupillometer (PLR-200, NeurOptics, Irvine, CA) in constant room lighting. Oxygen saturation, blood pressure and heart rate were collected using an automated monitor (DINAMAP PRO Series 400N V2, GE Medical Systems, Milwaukee, WI).

Subject-rated measures—Subject-rated measures included a Street Value Questionnaire and a series of items rated on a 100-unit visual analog scale (VAS). The items included in the VAS were: “Abdominal Pain,” “Agitated,” “Any Effect”, “Bad Effects,” “Blurred Vision,” “Decreased Appetite,” “Dizzy,” “Drowsy,” “Dry Mouth,” “Flushed,” “Good Effects,” “Headache,” “High,” “Like the Drug,” “Nauseous,” “Nervous,” “Relaxed,” “Sick,” “Sleepy,” “Sluggish, Fatigued or Lazy,” “Stimulated,” “Sweating,” “Twitching,” “Weak,” “Willing to Pay for the Drug” and “Willing to Take the Drug Again.” Items were selected for their sensitivity to the effects of mu opioid agonists (Stoops et al., 2012; Walsh et al.,

2008) or of norepinephrine and serotonin reuptake inhibitors (Heil et al., 2002; Jasinski et al., 2008; Vanderkooy et al., 2002).

Performance tasks—A computerized Digit Symbol Substitution Task (DSST; McLeod et al., 1982) was included as a performance task, with percent of trials completed correctly selected as the outcome variable.

Statistical Analysis

Results were considered significant for $p < 0.05$. All measures were first analyzed as raw time course data using a two-factor repeated measures analysis of variance with Dose and Time as the factors (StatView 5.0.1, SAS Institute, Cary, NC). Dunnett's post hoc tests were used to compare scores between active doses and placebo at each time point if a significant main effect of Dose or an interaction of Dose and Time was observed. When a significant interaction of Dose and Time was observed, significant main effects are not reported. Outcomes with only a significant main effect of Time also are not reported.

In addition, peak effects analyses (either trough or maximum depending upon the direction of effects) were completed using a one-factor ANOVA with Dose as the factor (StatView 5.0.1, SAS Institute, Cary, NC). Raw values were used to calculate peak effect, with trough defined as the lowest value observed after drug administration and maximum defined as the highest value observed after drug administration. Dunnett's post hoc tests were used to compare peak scores between active doses and placebo.

Results

Subjects

Eleven adult past-year recreational opioid users were enrolled in the protocol. Nine subjects completed the protocol. One of the two non-completing subjects was lost to follow up prior to receiving any doses, the other subject moved out of state prior to completing the study. Only data from the nine completers (seven male, two female) were included in the analyses. Seven subjects were White (one Hispanic), one was Black and one was Western Asian. Subjects were 24 ± 1 (mean ± SEM) years old. All reported recreational use of prescription opioids in the year prior to screening (an inclusion criterion), with oxycodone and hydrocodone combination products being the most commonly used. As estimated from screening materials, subjects reported using opioids for recreational purposes 23 ± 6 times in the past year. Six subjects reported current opioid use, with 3 ± 1 days using out of the past 30. For seven subjects, the preferred route of opioid administration was oral. For two subjects, the preferred route of opioid administration was intranasal. Eight subjects reported current alcohol use (9 ± 4 drinks in the week prior to screening) and seven were daily cigarette smokers. All subjects reported lifetime amphetamine use, eight subjects reported lifetime marijuana use and benzodiazepine use, six subjects reported lifetime cocaine use and hallucinogen use.

Time Course

Physiological Measures—Significant interactions of Dose and Time were observed on pupil diameter and diastolic blood pressure ($F_{54,432}$ values > 1.5, p values < 0.05). The top panels in Figure 1 show that all three drugs produced time-dependent, but generally not dose-dependent, decreases in pupil diameter with effects evident within 1 hr of dosing for hydromorphone and the low tapentadol dose and 2 hr of dosing for the other tapentadol doses and tramadol. Miotic effects of the drugs persisted throughout the remainder of the 6 hr session. The low doses of tapentadol and hydromorphone produced transient increases in diastolic blood pressure (data not shown). There were no significant main effects of Dose or

interactions of Dose and Time observed on other physiological measures, including the respiratory measure, oxygen saturation.

Subject-rated measures—Significant main effects of Dose and Time were observed on the Street Value Questionnaire ($F_{9, 72}$ = 2.1, p = 0.04, $F_{5,40}$ = 2.7, p = 0.04, respectively; Figure 2). The high dose of all drugs, as well as lower doses of tramadol and hydromorphone, produced comparable increases in ratings of street value. Effects were evident 1–2 hr after dosing and generally persisted through the remainder of the 6 hr session.

Significant interactions of Dose and Time were observed on 11 items from the VAS: "Abdominal Pain," "Any Effect," "Bad Effects," "Blurred Vision," "Good Effects," "Like the Drug," "Nauseous," "Sleepy," "Sweating," "Twitching" and "Willing to Take Again" ($F_{54,432}$ values > 1.3, p values < 0.05). Figure 1 shows two outcomes, "Good Effects" (middle panels) and "Bad Effects" (bottom panels). The high dose of all three drugs produced quantitatively similar increases in ratings of "Good Effects" with effects evident most rapidly for tapentadol, followed by hydromorphone, then tramadol. Effects offset most rapidly for tapentadol (i.e., ratings were only significantly different from placebo from 1–3 hr after dosing), and dissipated by the end of session for the other two drugs. Lower doses of tramadol and hydromorphone also increased ratings of "Good Effects" at a magnitude comparable to that observed for the high doses. Similar outcomes were observed for other items indicative of positive effects: "Like the Drug" and "Willing to Take Again," as well as for "Any Effect" (data not shown). Only tramadol increased ratings of "Bad Effects," with effects evident for the high dose 2 hr after dosing and dissipating 1 hr prior to the end of session. Similar outcomes were observed for ratings of "Nauseous" (data not shown). The low dose of tramadol transiently increased ratings on other items indicative of negative effects: "Abdominal Pain" and "Twitching" (data not shown). Transient increases were observed for the intermediate and high tapentadol doses and the high tramadol and hydromorphone doses on ratings of "Sleepy" (data not shown). Transient increases also were observed for the high tramadol and hydromorphone doses on ratings of "Blurred Vision" and "Sweating" (data not shown). There were no significant main effects of Dose or interactions of Dose and Time observed on other subject-rated measures.

Performance task—There were no significant effects on percent of trials completed correctly on the DSST.

Peak Effects

Table 1 (Supplementary Materials) presents F values, as well as mean (SEM), for outcomes from the peak effects analysis for which a statistically significant effect was observed in the ANOVA.

Physiological Measures—A significant effect of Dose was observed on pupil diameter. The low and high doses of tapentadol, as well as the two higher doses of tramadol and all doses of hydromorphone, significantly reduced pupil diameter relative to placebo. As with the Time Course Data, miosis was generally not dose-dependent. There were no significant effects of Dose on other physiological measures, including oxygen saturation.

Subject-rated measures—A significant effect of Dose was observed on the Street Value Questionnaire, but no active doses signficantly differed from placebo following *post hoc* analysis. Significant effects of Dose were observed on 5 items from the VAS: "Any Effect," "Bad Effects," "Good Effects," "Like the Drug" and "Relaxed." Relative to placebo, the high dose of tapentadol increased ratings on all measures except "Bad Effects." Relative to placebo, the high dose of tramadol increased ratings of "Any Effect," "Bad Effects," and

"Relaxed." Relative to placebo, the high dose of hydromorphone increased ratings of "Like the Drug." There were no significant main effects of Dose observed on other subject-rated measures.

Performance task—There was no significant effect on percent of trials completed correctly on the DSST.

Discussion

This study assessed the non-analgesic pharmacodynamic effects of tapentadol in occasional opioid users. The key findings of the study were: 1) 75 mg tapentadol produced protypic mu opioid agonist effects (e.g., miosis, increased ratings of "Like the Drug" and "Good Effects") that were similar to those of hydromorphone; 2) tramadol differed from tapentadol and hydromorphone because, in addition to producing miosis and positive subject-rated effects, it also produced low magnitude, but statistically significant, negative subject-rated effects (e.g., "Bad Effects). This finding is consistent with the notion that tramadol has a somewhat distinct profile of subject-rated effects relative to prototypic opioid analgesics (Babalonis et al., 2012; Epstein et al., 2006; Lofwall et al., 2007; Stoops et al., 2012); 3) hydromorphone produced mioisis and increased positive subject-rated effects, consistent with previous findings (Duke et al., 2011; Shram et al., 2010; Stoops et al., 2012; Walsh et al., 2008); 4) as has been observed previously (Abreu et al., 2001; Stoops et al., 2010; Walsh et al., 2008), the physiological effects (i.e., miosis; it is important to note that no drugs altered the respiratory measure, oxygen saturation) of all three drugs persisted longer than the subject-rated effects. The exception to this trend was street value estimates. The persistent increases observed for street value estimates may be due to an overall evaluation of drug effects that is not sensitive to time in the manner that other subject-rated effects are.

The miosis observed following administration of the three tapentadol doses was comparable to that observed for tramadol and hydromorphone, indicating that approximately equi-effective doses were administered. However, miosis was generally not dose-dependent and pupil diameter was not measured in a darkened room, which could have limited the miotic effects observed. The magnitude of reductions observed for pupil diameter were comparable to those reported for 64 mg tapentadol in the Australian technical report (Australian TGA, 2011). However, for subject ratings, the lower doses of tapentadol were generally placebo-like, in contrast to what was observed for lower doses of tramadol and hydromorphone in the time course analysis, which also increased positive subject-rated effects. The lack of effect observed for lower tapentadol doses could be due to the fact that all tapentadol doses fell in the acute therapeutic range whereas only the lower doses of tramadol and hydromorphone fell in that range (e.g., Afilalo et al., 2010; Beaulieu et al., 2007; Frampton, 2010; Grosset et al., 2005). Importantly, however, in the peak effects analysis, only the high doses of the tested drugs significantly increased subject-rated effects relative to placebo, likely due to reduced degrees of freedom in that type of analysis (Stoops et al., 2012), with 75 mg tapentadol producing increases on the greatest number of ratings and generally of the greatest magnitude. These findings stand in contrast somewhat with those of the Australian technical report, which showed that doses as low as 50 mg tapentadol significantly increased positive subject-rated effects 1 to 2 hr after dosing and overall liking ratings 24 hr after dosing in a manner similar to 4 mg hydromorphone (Australian TGA, 2011). That report also indicated that tapentadol and hydromorphone produced negative subject-rated effects 2 to 6 hr after dosing; negative subject-rated effects were not observed for those drugs in this study. The reasons for the discrepancies between the present study and those described in the Australian technical report are unclear given the limited level of detail available in that report. The discrepancies are outweighed, however, by the general agreement between the two studies regarding the similar miotic and positive subject-rated constellation of effects

produced by both tapentadol and hydromorphone. The present findings also indicate that pupil diameter may be more sensitive to mu opioid agonist effects than subject ratings because miosis was observed for drug doses that did not produce increases in subject-rated effects.

The positive effects (e.g., “Good Effects” and “Like the Drug”) of tapentadol were evident sooner than those of tramadol or hydromorphone; the effects also dissipated more rapidly than for the other two drugs. A rapid onset and offset of effects might lead to greater frequency of use; systematically changing rate of onset of effects alters the positive subject-rated effects of drugs, as well as drug self-administration (e.g., Comer et al., 2009; Kollins et al., 1998). However, the effects of supra-therapeutic doses of tapentadol need to be tested to better determine whether a rapid onset/offset of effects occur in a broader range of doses. Taken together, the findings that an oral, acute, therapeutic dose of tapentadol produces a rapid increase in positive subject-rated effects, with no negative effects observed (although whether supra-therapeutic tapentadol doses produce negative effects remains to be determined), have important implications for how tapentadol is prescribed, particularly to those with histories of substance misuse or use disorders.

Tramadol produced a profile of effects similar to what has been shown previously in nondependent opioid users (Duke et al., 2011; Stoops et al., 2012; Zacny, 2005). For example, tramadol produced miosis in a time course that was consistent with the pharmacokinetics of the M1 metabolite, which has greater affinity for mu opioid receptors than the parent drug (i.e., maximal effects were observed up to 5 hours after dosing; Lofwall et al., 2007; Stoops et al., 2012). Tramadol was the only tested drug that produced negative subject-rated effects here, in a time course that was more consistent with the pharmacokinetics of the parent drug, which is also similar to previous findings (Babalonis et al., 2012; Lofwall et al., 2007; Stoops et al., 2012). These effects were of lower magnitude than the positive effects. Moreover, given recent data indicating similar reinforcing effects of oxycodone and tramadol (Babalonis et al., 2012), the negative effects produced by tramadol may have limited impact on actual drug taking behavior. It is tempting to speculate about which of the differences between tapentadol and tramadol led to the divergent profiles of the two drugs in terms of negative subject-rated effects (e.g., dose, limited mu opioid receptor affinity of tramadol, serotonin reuptake inhibition effects of tramadol; Raffa et al., 2012), however, more research is necessary to determine which of these factors (or interactions of these factors) resulted in this outcome.

There are several limitations to the present experiment that should be acknowledged. First, relatively low doses of the drugs were tested (i.e., the majority were in the acute therapeutic range), which likely resulted in the small magnitude of effects observed and the lack of dose-related effects observed. These doses were selected to enhance safety for this lightly opioid-experienced population because they likely would not have the level of tolerance heavier users (e.g., Stoops et al., 2012; Walsh et al., 2008) have developed. In fact, tramadol doses more than two-fold higher administered to more opioid experienced individuals produced comparable increases in ratings to those observed in the present experiment for “Good Effects,” while also producing nausea and vomiting in some subjects (Stoops et al., 2012). Thus, higher doses in this study could have produced even greater increases in subject ratings, but also could have resulted in untoward effects due to reduced tolerance in the population tested here. Nonetheless, the selected doses did produce statistically significant increases on the outcome measures in a manner consistent with our hypotheses (i.e., tapentadol, hydromorphone and tramadol produced prototypic mu opioid physiological and subject-rated effects; tramadol also produced low magnitude negative subject-rated effects). Future research should test higher tapentadol doses in more experienced opioid users. Other research should determine the pharmacological mechanisms that contribute to

tramadol's negative subject-rated effects that make it somewhat distinct from tapentadol and prototypic opioids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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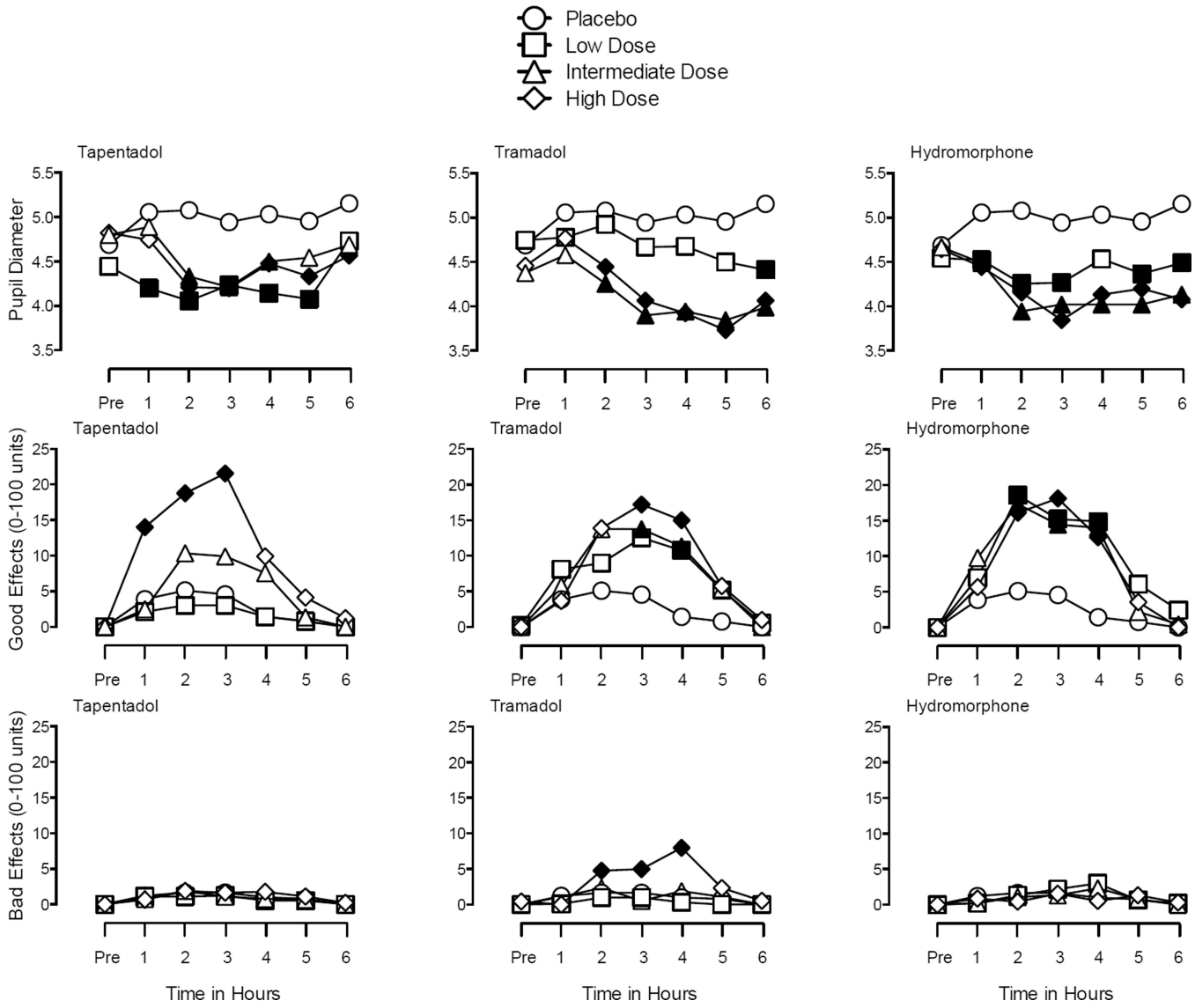

Fig. 1.

Data are shown for mean values (n=9) for pupil diameter for oral placebo (circles) and doses of tapentadol (25 mg: squares, 50 mg: triangles, 75 mg: diamonds), tramadol (50 mg: squares, 100 mg: triangles, 150 mg: diamonds) and hydromorphone (2 mg: squares, 4 mg: triangles, 6 mg: diamonds) on Pupil Diameter (top panels), ratings of "Good Effects" (middle panels) and ratings of "Bad Effects" (bottom panels) as a function of time (X-axis) since drug administration in the 6-hr session. Error bars omitted for clarity. Filled symbols indicate a significant difference from the corresponding PLB time point

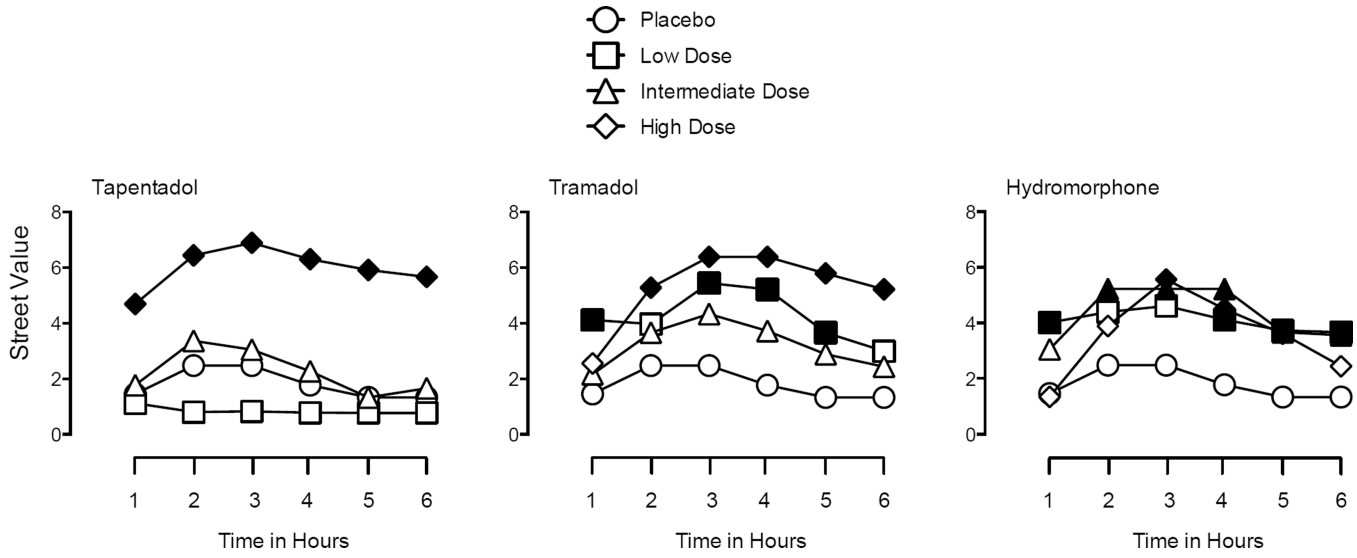

Fig. 2.

Data are shown for mean values (n=9) for Street Value estimates. All other details are the same as for Figure 1