The Analgesic Effect of Tramadol After Intravenous Injection in Healthy Volunteers in Relation to CYP2D6

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Tramadol analgesia results from a monoaminergic effect by tramadol itself and an opioid effect of its metabolite (+)-M1 formed by O-demethylation of tramadol by CYP2D6. In this study we sought to determine the impact of (+)-M1 on the analgesic effect of tramadol evaluated by experimental pain models. The effect of an IV injection of 100 mg tramadol on experimental pain was studied 15–90 min after dosing in volunteers, 10 extensive metabolizers with CYP2D6 and 10 poor metabolizers without CYP2D6 in 2 placebo-controlled trials. The pain tests included detection and tolerance threshold to single electrical sural nerve stimulation, pain summation threshold to repetitive electrical sural nerve stimulation (temporal summation), and the cold pressor test. In extensive metabolizers, tramadol reduced discomfort experienced during the cold pressor test ($P = 0.002$). In poor metabolizers, the pain tolerance thresholds to sural nerve stimulation were increased ($P = 0.04$). (+)-M1 could be detected in the serum samples from all extensive metabolizers except one, but (+)-M1 was below the limit of determination in all poor metabolizers. The opioid effect of (+)-M1 appears to contribute to the analgesic effect of tramadol, but the monoaminergic effect of tramadol itself seems to create an analgesic effect.

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The analgesic drug, tramadol, has a dual mechanism of action, a monoaminergic effect by tramadol itself and an opioid effect mediated by the metabolite M1 (1,2). (+)-tramadol has mainly a noradrenergic and (−)-tramadol a serotonergic effect (1). The opioid effect is thought to result exclusively from the plus isomer of M1.

The O-demethylation of tramadol to (+)-M1 is catalyzed by CYP2D6 (2,3). There is genetic polymorphism with respect to this P450 enzyme. Approximately 7% of Caucasians lack CYP2D6 and are considered to be poor metabolizers (4). The remaining 93% have the enzyme and are extensive metabolizers. Sparteine, which was formerly used as an antiarrhythmic drug, is used to detect the phenotypic poor and extensive metabolizers because the metabolic ratio (MR) between sparteine and the metabolites formed by O-demethylation via CYP2D6 can be used to categorize the individuals into extensive ($MR < 20$) and poor metabolizers ($MR \geq 20$) (5).

We have previously studied the analgesic effect of an oral dose of tramadol 2 mg/kg body weight in panels of extensive metabolizers of sparteine with CYP2D6 and poor metabolizers without the enzyme (2). The analgesic effect, as evaluated by human experimental pain models up to 10 h after dosing, was much weaker in the poor metabolizers than in the extensive metabolizers. This confirmed the contribution of the opioid effect of (+)-M1 to the analgesic effect of tramadol, as (+)-M1 was not formed in the poor metabolizers.

Tramadol is also available as an IV formulation for use in acute (e.g., postoperative) pain (6). The impact of metabolizer phenotype in this situation, in which first pass metabolism in the liver is bypassed, is unknown. The aim of the present experimental study was to investigate the analgesic effect of an IV bolus injection of tramadol in human experimental pain models in randomized, double-blind, placebo-controlled trials in extensive and poor metabolizers of sparteine.

Methods

Ten extensive metabolizers of sparteine with MR 0.1–0.8 and 10 poor metabolizers with $MR \geq 20$ (7) were

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selected from among more than 2000 healthy volunteers phenotyped with respect to sparteine metabolism at the Department of Clinical Pharmacology, University of Southern Denmark. The extensive metabolizer group included 4 men and 6 women (age range, 21 to 30 yr); the poor metabolizer group included 6 men and 4 women (age range, 22 to 33 yr). The volunteers were not allowed to consume alcohol or analgesics, except for study medication, 24 h before and during study days. The volunteers gave written informed consent before the study procedure, and the study was approved by the Regional Scientific Ethical Committee of Vejle and Funen Counties (J. No. 1998-0033) and the Danish Medicines Agency (J. No. 2612-346).

The two phenotype groups were studied in randomized, balanced, double-blind, placebo-controlled, crossover trials at the same location and time by the same researchers. The treatments were single IV bolus injections (injected over 5 min) of saline (placebo) and 100 mg tramadol. Study medication had identical appearance and was provided by the manufacturer (Grünenthal GmbH, Germany) in vials packed in boxes labeled with subject number and study phase. The subjects were numbered consecutively as they entered the study. These numbers corresponded to the randomization numbers on the boxes with study drugs, as generated by the manufacturer by a computer program. The two study days were separated by a washout period of at least 1 wk. On each study day, nociceptive tests as described below were performed before medication and 15, 30, 60, and 90 min after medication.

At study inclusion, the volunteers were familiarized with the nociceptive tests and on each study day the tests were performed once again before actual study measurements were performed.

The percutaneous electrical stimulation of the sural nerve along its retromalleolar path by a constant-current rectangular pulse consisted of 5 pulses (each of 1 ms duration) delivered at 200 Hz (single stimulation) or this stimulus burst repeated 5 times with a frequency of 3 Hz (repetitive stimulation) to investigate temporal summation. Psychophysical pain detection and tolerance thresholds were determined to single stimulation (8). Pain summation threshold was defined as the stimulus strength at which pain clearly increased through the 5 stimulations and was unequivocally painful at the last 1 or 2 stimulations (8,9).

The left hand was immersed into ice-chilled water (1.0°C ± 0.3°C) that was continuously stirred by a pump. After 2 min of immersion—or sooner if the pain was considered intolerable—the subject removed his/her hand from the water. Pain intensity was continuously rated during the test by use of an electronic visual analog scale coupled to a computer. From the data obtained, peak pain intensity was determined (10). Immediately after the test, the subjects rated the discomfort experienced during the procedure on a visual analog scale.

Blood for determination of serum drug concentrations was drawn after each nociceptive test session on both study days. The concentration of (+)- and (−)-tramadol and (+)- and (−)-M1 was determined with a modification of a gas chromatographic method, as described previously (2,11).

Sums of differences between premedication and postmedication values of pain measures were calculated for tramadol and placebo for each subject for each of the pain measures as a summary measure of effect. The sums of differences were compared by use of the Wilcoxon test for paired differences. The relation between response (the difference between the effect of tramadol and placebo) and drug levels as given by area under the concentration time curve from 0 to 90 min ($AUC_{0\text{-}90}$) were tested with the Spearman rank correlation test.

Differences in the response on the pain measures (median differences between tramadol and placebo) and in serum concentrations of (+)- and (−)-tramadol and +(-) and (−)-M1 between the two groups of phenotypes were tested by use of the Mann-Whitney *U*-test (Wilcoxon two sample test) at each postmedication test time.

Results

The sums of differences for each pain measure for the two phenotypes and the corresponding significance testing are presented in Table 1. Figures 1 and 2 show the median difference with 95% confidence intervals between tramadol and placebo for the pain measures indicating statistical significance at each postmedication test time as described by Campbell & Gardner (12). A significant difference in discomfort between the two groups of phenotypes was found at 90 min after medication during the cold pressor test ($P < 0.02$).

In extensive metabolizers, discomfort during the cold pressor test was significantly reduced by tramadol ($P = 0.002$), whereas peak pain during the test was unchanged. Tramadol did not significantly alter pain detection and tolerance threshold or pain summation threshold after sural nerve stimulation.

In poor metabolizers, pain tolerance threshold to single sural nerve stimulation was significantly increased by tramadol compared with placebo ($P = 0.04$), whereas no other pain measure was changed.

Figure 3 shows the concentration of (+)- and (−)-tramadol and of (+)- and (−)-M1 in the two phenotypes during the study. No significant difference in the concentrations of the tramadol enantiomers was found comparing the two groups of phenotypes. (+)-M1 concentrations were below the limit of determination in all poor metabolizers, whereas in extensive metabolizers they ranged from below the limit of

Table 1. Median Values of Sums of Differences for the Different Pain Measures and Significance Testing

	Tramadol	Placebo	*P* value
Extensive metabolizers			
Cold pressor test			
Peak pain (cm)	−3.2	−2.0	0.25
Discomfort (cm)	−2.6	−0.3	0.002
Electrical sural nerve stimulation			
Pain detection threshold (mA)	4.5	5.3	0.96
Pain tolerance threshold (mA)	9.8	6.0	0.27
Pain summation threshold (mA)	1.9	2.5	0.73
Poor metabolizers			
Cold pressor test			
Peak pain (cm)	0.0	0.0	0.13
Discomfort (cm)	−0.1	1.4	0.16
Electrical sural nerve stimulation			
Pain detection threshold (mA)	5.0	3.8	0.32
Pain tolerance threshold (mA)	13.3	3.8	0.04
Pain summation threshold (mA)	2.7	2.0	0.63

The sums of differences are sums of premedication minus postmedication values for each drug.
P values by Wilcoxon test for paired differences.

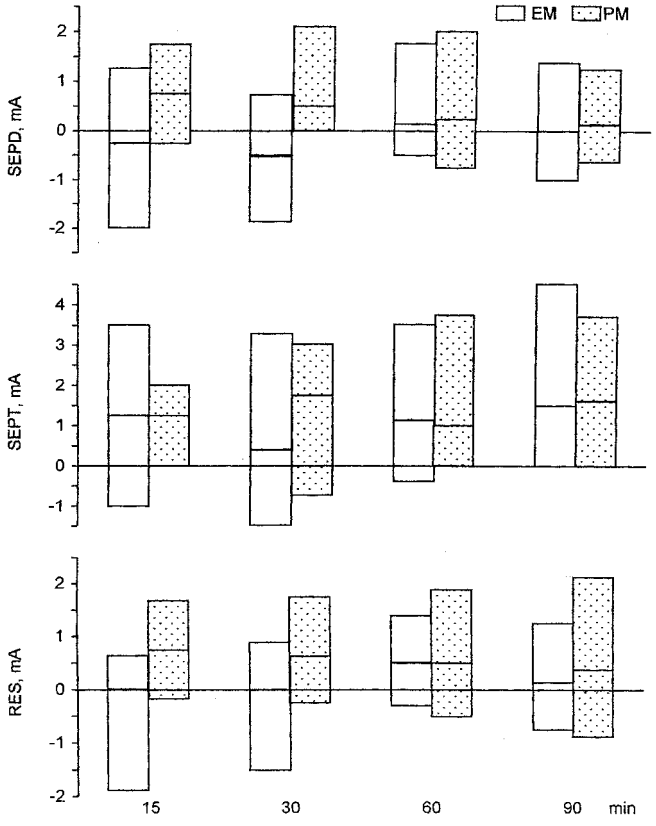

Figure 1. Median difference (horizontal line) with 95% confidence interval (box) between tramadol and placebo of the change in pain detection (SEPD) and tolerance (SEPT) thresholds after single electrical sural nerve stimulation and pain summation threshold after repetitive electrical sural nerve stimulation (RES) at different times after dosing. *Open bars*, extensive metabolizers; *dotted bars*, poor metabolizers.

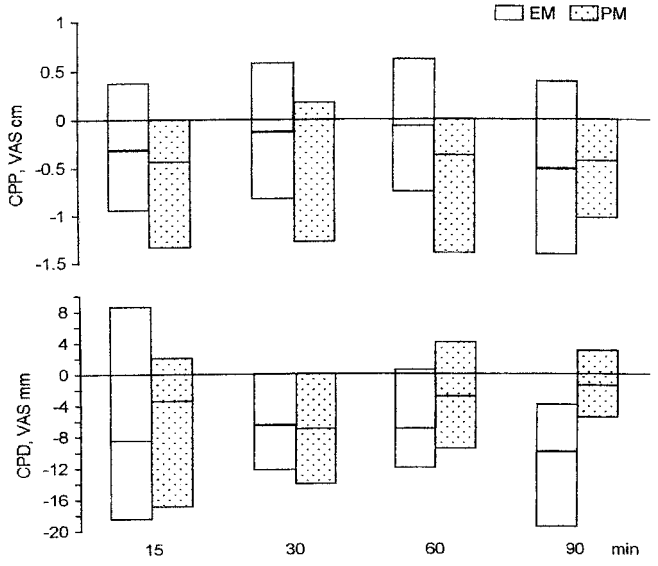

Figure 2. Median difference (horizontal line) with 95% confidence interval (box) between tramadol and placebo of the change in peak pain (CPP) and discomfort VAS rating (CPD) during the cold pressor test at different times after dosing. *Open bars*, extensive metabolizers; *dotted bars*, poor metabolizers.

determination at all times in one subject to 30 ng/mL (Fig. 4). (−)-M1 concentrations were below limit of determination at all measurements in 6 of 10 poor metabolizers and ranged from 5.5 ng/mL to 29 ng/mL in extensive metabolizers (Fig. 4). At all measurements, the concentrations of (+)-M1 and (−)-M1 were found to be significantly larger in the extensive than in the poor metabolizers ($P < 0.01$ at 15 min and $P < 0.001$ at 30, 60, and 90 min).

There was no significant relation between the sums of differences for the pain measures and the corresponding $AUC_{0\text{-}90}$ for the sum of tramadol enantiomers in any of the phenotypes. There was a positive correlation between the reduction in peak pain intensity during the cold pressor test and $AUC_{0\text{-}90}$ of

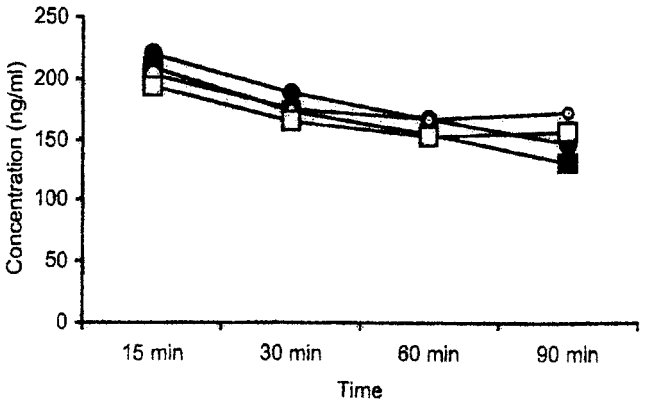

Figure 3. Mean serum concentration of (+)-tramadol (●, ○) and (−)-tramadol (■, □) in 10 extensive (●, □) and 10 poor (○, □) metabolizers of sparteine after a bolus injection of 100 mg tramadol.

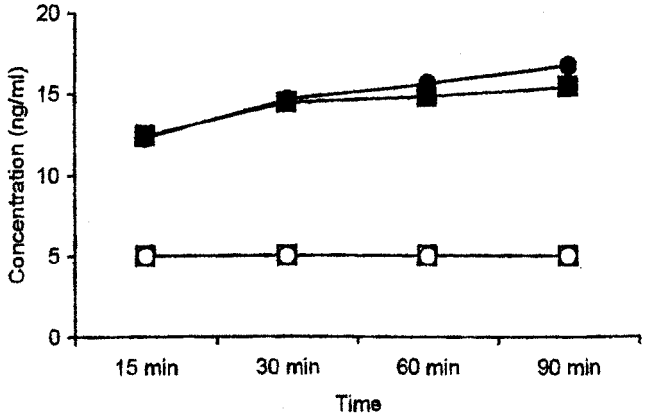

Figure 4. Mean serum concentration of (+)-M1 (●, ○) and (−)-M1 (■, □) in 10 extensive (●, ■) and 10 poor (○, □) metabolizers of sparteine after a bolus injection of 100 mg tramadol. Concentrations below the limit of determination of the assay (5.1 ng/mL) set to 5 ng/mL.

(+)-M1 in extensive metabolizers ($r_s = -0.758$; $P < 0.02$) as shown in Figure 5.

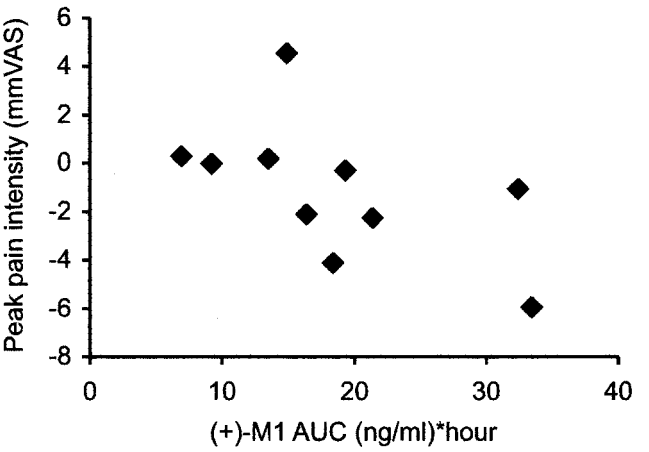

Figure 5. Correlation between the effect of tramadol versus placebo on peak pain intensity (mm VAS) during the cold pressor test and the AUC of (+)-M1 (0–90 min). A negative value in mm VAS indicates a reduction of peak pain intensity in favor of tramadol.

Discussion

In this human experimental pain study, we found that, in extensive metabolizers of sparteine, there was a reduction of discomfort during the cold pressor test within 90 minutes after IV injection of 100 mg tramadol. The decrease in peak pain intensity during the cold pressor test and the AUC from 0 to 90 minutes of serum concentration of tramadol's metabolite (+)-M1 were correlated. In contrast, in poor metabolizers, tramadol caused an increase in pain tolerance threshold to sural nerve stimulation but no effect in the cold pressor test. Therefore, the present results further support the importance of the opioid effect of (+)-M1 for the analgesic effect of tramadol. They also indicate that the monoaminergic mechanisms of the parent compound contribute to the action, as there is some effect in poor metabolizers.

The less pronounced and equivocal analgesic effect of tramadol in the same experimental pain models, which in our previous study (2) revealed clear-cut changes in extensive metabolizers, may be explained by several factors. First, in the present study, extensive metabolizers had substantially smaller serum concentrations of (+)-M1 (range, 5–30 ng/mL) than in the previous study (range, 20–60 ng/mL). This is probably because the present study, in contrast to the previous one, used IV dosing in which first-pass metabolism does not take place. Second, we only measured the analgesic effect until 90 minutes after dosing, whereas our previous study (oral dosing) tested the effect for 10 hours and found a maximal effect on pain after sural nerve stimulation 4 to 6 hours after dosing (2). The small (+)-M1 concentration may be most important in the cold pressor test, which is opioid sensitive (10) and probably relatively insensitive to the monoaminergic effects, as we have seen for drugs such as imipramine and venlafaxine (8,13,14). A larger dose of tramadol in this study could possibly have shown more pronounced analgesic effects in the pain models, but the chosen dose is similar to the recommended treatment for postoperative pain. Therefore, a dose of 100 mg tramadol given IV creates a realistic picture of the impact of CYP2D6 in the postoperative analgesia from tramadol.

The pain tolerance threshold to sural nerve stimulation may be suited for detecting the analgesia from the monoaminergic effect of tramadol itself, as it is seen in both extensive and poor metabolizers and it is also obtained with the monoaminergic antidepressants imipramine and venlafaxine (2,8,13,14). The serum concentrations of tramadol enantiomers were similar in this and our previous tramadol study, but

here the time effect could be the crucial factor. The data analysis showed that the extensive metabolizers did not have a significant analgesic effect in the sural nerve stimulation. This can hardly be explained by pharmacokinetic differences between the two groups of volunteers, as the concentrations of tramadol in the serum samples from the extensive metabolizers were similar to those from the poor metabolizers. However, the concentrations of tramadol and (+)-M1 in the deep compartment of the central nervous system could be different from the concentrations found in the peripheral blood as the result of biotransformation to (+)-M1 in the brain, as CYP2D6 is expressed in human brain tissue (15). An increase in effect at a time when the drug concentrations decrease, as found in the previous study (2), indicates that tramadol may have to penetrate into a deep compartment of the central nervous system to exert its effects.

In extensive metabolizers, tramadol has to be metabolized to (+)-M1 to exert its full effect and the fraction of the population being poor metabolizers (approximately 7% of Caucasians) may not be adequately pain relieved via the opioid effect but may still benefit from the monoaminergic effect. In one study, poor metabolizers experienced less postoperative pain relief with tramadol than extensive metabolizers (16). The need for rescue medication in the form of opioids was significantly larger among the poor metabolizers than among the extensive metabolizers, which is fully in line with our previous and present experimental data.

Among the extensive metabolizers, there may also be reduced analgesic effect as a result of drug-drug interactions when the biotransformation of (+)-M1 is blocked with inhibitors of CYP2D6, such as some selective serotonin reuptake inhibitors (17).

Data from this study contribute further evidence that the biotransformation of tramadol to the metabolite (+)-M1 via CYP2D6 has a major impact on the analgesic effect of tramadol, as (+)-M1 appears to create the opioid effect of tramadol. However, the monoaminergic effect of the parent compound itself seems to have an analgesic effect.

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