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Effects of Celecoxib and Etoricoxib on the Pharmacokinetics and Pharmacological Effects of Orally Administered Tramadol: A Randomised Controlled Trial

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ABSTRACT

Tramadol is a widely used analgesic whose bioactivation to O-desmethyltramadol is primarily mediated by cytochrome P450 2D6 (CYP2D6). Genetic variability and drug–drug interactions affecting CYP2D6 may influence tramadol pharmacokinetics and pharmacological effects. Cyclooxygenase-2 inhibitors are frequently co-administered with tramadol in multimodal analgesia, but their potential to affect tramadol disposition and effects remains incompletely characterised. Celecoxib has been reported to act as a weak inhibitor of CYP2D6 in vivo. This randomised, single-blind, placebo-controlled crossover study evaluated the effects of 8-day pretreatment with celecoxib or etoricoxib (200 and 120 mg once daily, respectively), compared with placebo, on the pharmacokinetics and pharmacological effects of a single 100 mg oral dose of tramadol in 12 healthy volunteers. Plasma concentrations of tramadol and O-desmethyltramadol were measured, and pharmacological effects were assessed using visual analogue scales, psychomotor testing (digit symbol substitution test) and cold pressor pain models. Celecoxib pretreatment did not change tramadol exposure but reduced the formation of O-desmethyltramadol, decreasing the geometric mean AUC ratio (GMR) of O-desmethyltramadol to tramadol (AUC_m/AUC_p) by 24% relative to placebo (90% CI, 0.69–0.84; $p < 0.001$). Etoricoxib had minimal effects on tramadol exposure or metabolism (GMR 0.92; 90% CI, 0.84–1.02; $p = 0.13$). In conclusion, celecoxib modestly inhibited the bioactivation of tramadol, but not etoricoxib. Differences in pharmacological effects were negligible.

1 | Introduction

Tramadol is a centrally acting analgesic widely used for the treatment of acute and chronic pain [1–4]. It exerts its analgesic effects through a dual mechanism, combining weak μ-opioid receptor agonism by the parent compound and the active metabolite O-desmethyltramadol and by inhibition of neuronal reuptake of serotonin and noradrenaline by the

Tuukka Saarikoski and Teijo I. Saari have equal contribution.

[†]Prof. Neuvonen passed away before the final approval of this manuscript.

Summary

This study examined whether two commonly used anti-inflammatory pain medicines, celecoxib and etoricoxib, influence how the body processes tramadol, an opioid analgesic. In a randomised crossover study, 12 healthy volunteers received tramadol after pretreatment with celecoxib, etoricoxib or placebo. Celecoxib slightly reduced the formation of tramadol's active metabolite, whereas etoricoxib had little effect. However, these pharmacokinetic changes did not lead to meaningful differences in drug effects, such as pain responses or psychomotor performance. Overall, the results suggest that tramadol can generally be used together with celecoxib or etoricoxib without clinically important drug interactions in people with normal metabolism of tramadol.

parent compound [5, 6]. Tramadol has demonstrated efficacy in several pain conditions, including neuropathic and postoperative pain [2–6].

Tramadol is considered a prodrug, as its primary active metabolite, O-desmethyltramadol, exhibits markedly higher affinity for the μ-opioid receptor than the parent compound [7]. The formation of O-desmethyltramadol is predominantly mediated by cytochrome P450 (CYP) 2D6. Consequently, both genetic variability in CYP2D6 and drug–drug interactions (DDIs) involving CYP2D6 inhibitors may substantially influence tramadol pharmacokinetics and clinical response [8, 9]. Reduced CYP2D6 activity has been associated with reduced O-desmethyltramadol exposure and diminished opioid-mediated analgesia [10, 11]. Moreover, poor CYP2D6 activity increases the exposure to parent tramadol and is a risk factor for serotonergic adverse effects [12].

Selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and etoricoxib, are frequently co-administered with opioids as part of multimodal analgesia strategies. Celecoxib has been shown to increase exposure to the CYP2D6 substrates dextromethorphan and metoprolol, consistent with weak CYP2D6 inhibition in vivo [13], but its effects on other CYP2D6 substrates remain poorly characterised. These observations raise the possibility of a clinically relevant interaction between celecoxib and tramadol. In contrast, etoricoxib has not been consistently associated with CYP2D6 inhibition. Although DDIs involving strong CYP2D6 inhibitors are well established, the clinical relevance of potential interactions between tramadol and COX-2 inhibitors remains uncertain.

Although celecoxib has been shown to increase exposure to selected CYP2D6 substrates, the magnitude and clinical relevance of its effect on tramadol bioactivation remain uncertain. Given the central role of CYP2D6 in the formation of O-desmethyltramadol, we hypothesised that celecoxib may modestly inhibit tramadol bioactivation, whereas etoricoxib would have minimal effects. The aim of this randomised crossover study was therefore to quantify the effect of repeated pretreatment with celecoxib or etoricoxib on the pharmacokinetics of tramadol and its active metabolite O-desmethyltramadol and to assess whether any pharmacokinetic changes translate into altered pharmacological effects.

2 | Materials and Methods

2.1 | Study Subjects

We enrolled 12 healthy non-smoking subjects to this study. All subjects were Caucasians of Finnish origin (8 males, 4 females, age 20–25 years and BMI 21.9 ± 2.3 kg/m^2). CYP2D6 genotype was unknown at the time of recruiting to this study. On the recruiting process, health of the subjects was confirmed by clinical examination, laboratory tests and electrocardiogram. Urine tests to screen for drugs of abuse and pregnancy test for females were negative. Females were instructed to use non-hormonal contraception during the study. A written signed consent was obtained from all subjects at the recruiting process. Potential for drug abuse was found to be low by the Finnish version of the Abuse Questions [14]. All use of medications were forbidden during and 2 weeks before the study, and drugs known to cause enzyme induction or inhibition were forbidden 30 days before the study. Tea, coffee, alcohol and cola drinks were forbidden during the study days. An approval was obtained from the Ethics Committee of the Hospital District of Southwest Finland and the Finnish National Agency for Medicines. The study was registered in the EudraCT register (EudraCT no.: 2010-023373-19) and the ClinicalTrials.gov register (NCT01304069, date of registration: 11.7.2011). The study was conducted according to the revised (2008) Declaration of Helsinki. All personal data were handled in accordance with the General Data Protection Regulation (EU 2016/679), and data were pseudonymised prior to analysis. This study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies [15].

2.2 | Study Design

This crossover study was conducted as single-blinded placebo controlled and randomised with three phases. Washout time between phases was 2 weeks. The order of treatments was randomised using a balanced 3 × 3 Latin square design generated by an independent statistician, ensuring that each treatment occurred equally often in each study period and minimising potential period effects. The study was conducted in the University of Turku research facility (Institute of Biomedicine, University of Turku, Turku, Finland). The subjects were given oral pretreatment for 8 days of celecoxib 200 mg at 07:00 a.m. and 07:00 p.m. or etoricoxib 120 mg at 07:00 a.m. and placebo at 07:00 p.m. or placebo at 07:00 a.m. and 07:00 p.m. The challenge dose of 100 mg tramadol orally was given on Day 7 of the pretreatment at 08:00 a.m. The hospital pharmacy (Pharmacy of the Hospital District of Southwest Finland, Turku, Finland) packed the study medications according to a randomisation list. Blood samples for analysis of tramadol and O-desmethyltramadol concentrations were taken from the forearm vein cannula immediately before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24 and 48 h after tramadol administration. Samples for celecoxib and etoricoxib concentration analyses were taken before administration of

tramadol. The subjects were instructed to fast 8 h before tramadol administration, and they were served standardised meals 4 and 8 h after tramadol.

2.3 | Bioanalytical Methods

The concentrations of plasma tramadol and O-desmethyltramadol were measured on an API 3000 liquid chromatography–tandem mass spectrometry system (AB Sciex, Toronto, ON, Canada) as previously described [16], with minor modifications. Prior to analysis, a simple protein precipitation of plasma samples with acetonitrile was performed, excluding the samples containing very low plasma drug concentrations (48-h samples), which were prepared by use of a MCX solid phase extraction (Waters, Milford, MA). Chromatography was performed on an Atlantis T3 analytical column (2.1 × 100 mm; Waters) using 10 mM formic acid with 0.1% (v/v) trifluoroacetic acid (Channel A) and methanol (Channel B) as the mobile phase. Tramadol-d6 and O-desmethyltramadol-d6 served as internal standards and were added to plasma samples, plasma quality control samples and plasma reference standards before other pre-analytical procedures. The recovery for both analytes were > 75%. The mass spectrometer was operated in positive multi-reaction monitoring (MRM+) detection mode with electrospray ionisation. The selected ion transitions used for quantification were: m/z 264 to m/z 58 for tramadol, m/z 250 to m/z 58 for O-desmethyltramadol and m/z 270 to m/z 64 and m/z 256 to m/z 64 for internal standards, respectively. The limit of quantification for plasma tramadol and O-desmethyltramadol was 0.02 ng/mL. The interday coefficients of variation (CV%) were for tramadol 7.2% at 2 ng/mL, 7.8% at 10 ng/mL and 4.6% at 100 ng/mL and for O-desmethyltramadol 4.9% at 1.75 ng/mL, 8.5% at 8.75 ng/mL and 5.4% at 87.5 ng/mL. The inter-day accuracy, expressed as the percentage relative error (RE%) from nominal concentrations (2, 10 and 100 ng/mL), was < 10%.

The plasma concentrations of celecoxib and etoricoxib were determined by reversed phase high-performance liquid chromatography (HPLC) using ultraviolet detection with rofecoxib as the internal standard [17, 18]. The limit of quantification was 20 ng/mL for celecoxib and 10 ng/mL for etoricoxib. The within-day CV was 6.8% at 25 ng/mL, 12.4% at 258 ng/mL and 1.5% at 863 ng/mL for celecoxib and 4.4% at 30 ng/mL, 4.6% at 296 ng/mL and 1.7% at 1038 ng/mL for etoricoxib ($n = 7$). The drugs did not interfere with the determination of each other.

2.4 | Pharmacokinetics

Peak plasma concentrations (C_{max}) and corresponding peak times (t_{max}) of tramadol and O-desmethyltramadol were observed directly from the plasma concentration data. For the determination of the AUC, the linear trapezoidal method was used when successive concentrations were increasing, and logarithmic trapezoidal method was used when decreasing. The ratio of metabolite to parent compound (AUC_m/AUC_p) was also calculated. The individual terminal log-linear phases of the concentration curves were identified visually. The elimination rate constant (k_e) was determined by regression analysis of the log-linear part of the curve. The elimination half-life ($t_{1/2}$) was then calculated using the equation $t_{1/2} = \ln 2/k_e$. The pharmacokinetic data were analysed by using the WinNonlin pharmacokinetic program (Version 4.1; Pharsight, Mountain View, CA).

2.5 | Pharmacological Effects

The subjective assessment of drug effect was acquired with a 100-mm-long visual analogue scale. Digit symbol substitution test (DSST) [19] was used to evaluate possible psychomotor effects. Analgesic effect was evaluated with cold pressor test [20]. In this test subject immersed hand in ice cold water (0.5°C–2°C) for 60 s. Intensity of pain was evaluated 30 (CPI30) and 60 (CPI60) seconds following immersion. Cold pain threshold (CPT) was defined as the time point when the cold water started to cause pain. These pharmacodynamic tests were carried out before and 1, 2, 3, 4, 5, 6, 8, 10 and 12 h after the administration of tramadol, and adverse effects were evaluated before and 3 and 6 h after tramadol administration. For each endpoint, the area under the effect–time curve from 0 to 12 h ($AUEC_{0-12}$) was calculated using the linear trapezoidal rule.

2.6 | CYP2D6 Genotyping

Genomic DNA was extracted from 6-mL whole blood EDTA samples using the Maxwell LEV Blood DNA Kit on a Maxwell 16 Research automated nucleic acid extraction system (Promega, Madison, WI). The samples were genotyped for the *CYP2D6*2*, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*6*, *CYP2D6*7*, *CYP2D6*8*, *CYP2D6*9*, *CYP2D6*10*, *CYP2D6*11*, *CYP2D6*15*, *CYP2D6*17*, *CYP2D6*18*, *CYP2D6*19*, *CYP2D6*20*, *CYP2D6*29*, *CYP2D6*35*, *CYP2D6*40* and *CYP2D6*41* alleles using a custom TaqMan OpenArray genotyping plate on a QuantStudio 12K Flex real-time PCR system (Life Technologies, Carlsbad, CA, USA) [21, 22]. The CYP2D6 copy number was determined with the TaqMan copy number assay Hs00010001_cn targeting exon 9 on the QuantStudio 12K Flex system. Activity scores and CYP2D6 metaboliser status were inferred from the observed genotypes [22, 23]. *CYP2D6* genotype data were summarised descriptively. Given the limited number of other than normal CYP2D6 metabolisers, genotype effects were evaluated descriptively only, and no formal covariate or subgroup analyses were performed.

2.7 | Statistical Analysis

In view of previous studies, it was calculated that 10 subjects would be required to demonstrate a 30% difference between the largest mean and the smallest mean in the area under the tramadol plasma concentration–time curve at a level of significance of $p = 0.05$ and power of 80% [24]. To prepare for dropouts, 12 healthy non-smoking subjects were enrolled. Primary outcome variables in this study were the area under plasma concentration–time curve ($AUC_{0-\infty}$) of tramadol. Shapiro–Wilk's test was used to examine the normality of the data. Analysis of variance for repeated measurements was used to analyse the differences in the pharmacokinetic variables in all randomised participants, except for t_{max}, which was analysed with Wilcoxon signed-rank test. Differences were considered statistically significant at $p < 0.05$. Pharmacokinetic results are reported as geometric mean ratios

with corresponding 90% confidence intervals (CI), and pharmacokinetic differences were interpreted in the context of commonly applied bioequivalence limits (0.80–1.25). Geometric mean ratios are expressed relative to placebo (treatment/placebo).

Pharmacological effects were evaluated using linear mixed-effects models with treatment as a fixed effect and subject as a random effect to account for the crossover design. For endpoints with strictly positive AUEC values, analyses were performed on the log-transformed scale, and results are presented as geometric mean ratios with 90% CI; for other endpoints, analyses were conducted on the original scale, and results are presented as mean differences with 90% CI. These analyses were considered exploratory, and emphasis was placed on estimation of effect size and CI rather than formal hypothesis testing.

Pharmacokinetic and pharmacological effects data were analysed using R (R Foundation for Statistical Computing, Vienna, Austria) [25] within the RStudio integrated development environment (Posit Software, Boston, MA, USA) [26].

3 | Results

All subjects completed the study. Mean (SD) plasma concentrations of celecoxib and etoricoxib were 548 (693) ng/mL and 622 (151) ng/mL in the respective study days. All subjects had meaningful coxib concentrations before tramadol intake, suggesting adequate compliance to the coxib pretreatment.

3.1 | *CYP2D6* Genotyping

CYP2D6 genotyping identified nine normal metabolisers, one intermediate metaboliser and two ultrarapid metabolisers among the 12 participants. Interindividual pharmacokinetic variability stratified by CYP2D6 phenotype is illustrated in Figure 2. Owing to the limited number of non-normal metabolisers, no genotype-stratified analyses were performed.

3.2 | Pharmacokinetics

Mean concentration–time profiles of tramadol and O-desmethyltramadol were similar across treatments (Figure 1). Pretreatment with celecoxib did not meaningfully alter tramadol exposure but reduced the exposure to the active metabolite O-desmethyltramadol by approximately 14% (geometric mean ratio for $AUC_{0-\infty}$ 0.86; 90% CI, 0.81–0.92; $p = 0.001$) (Table 1 and Figure 2). In addition, celecoxib significantly reduced the C_{max} of O-desmethyltramadol (geometric mean ratio 0.75; 90% CI, 0.71–0.78; $p < 0.001$). Despite statistical significance for several variables, the geometric mean ratios and corresponding 90% CI remained largely within commonly accepted bioequivalence limits. Etoricoxib pretreatment had no consistent effect on tramadol or O-desmethyltramadol exposure. O-Desmethyltramadol C_{max} was modestly lower after etoricoxib pretreatment (geometric mean ratio of 0.84; 90% CI, 0.79–0.90; $p = 0.001$), but no changes in overall exposure or elimination variables were observed (Table 1).

3.2.1 | Metabolite-to-Parent Exposure Ratio

To further characterise the relative formation of O-desmethyltramadol, the ratio of O-desmethyltramadol to tramadol exposure (AUC_m/AUC_p) was evaluated across treatment conditions. Compared with placebo, celecoxib pretreatment was associated with a statistically significant decrease in the AUC ratio, with a geometric mean ratio of 0.76 (90% CI, 0.69–0.84; $p < 0.001$), indicating reduced formation of O-desmethyltramadol. In contrast, etoricoxib pretreatment did not significantly alter the AUC ratio compared with placebo (geometric mean ratio of 0.92; 90% CI, 0.84–1.02; $p = 0.13$) (Table 1).

3.3 | Pharmacological Effects

Minor or moderate adverse effects were reported by nine subjects across treatment periods, most commonly drowsiness, dizziness and dry mouth. There were no serious adverse effects.

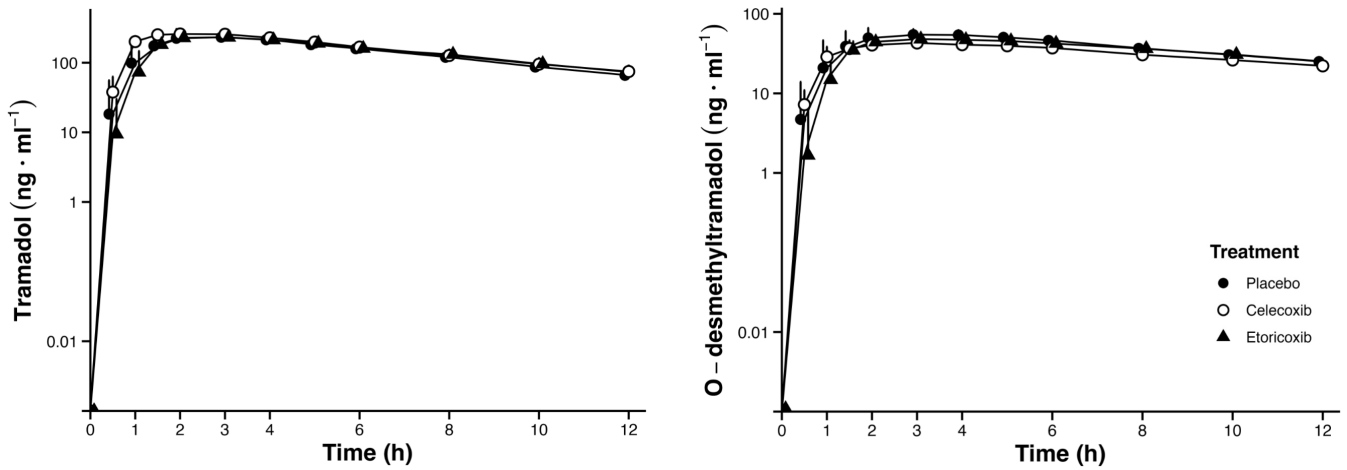

FIGURE 1 | Plasma concentration–time profiles (geometric mean and 90% CI) of tramadol (left panel) and O-desmethyltramadol (right panel) after a single oral dose of 100 mg tramadol following 8-day pretreatment with celecoxib (200 mg twice daily) or etoricoxib (120 mg once daily), compared with placebo in 12 healthy volunteers.

TABLE 1 | Pharmacokinetic variables of tramadol and its primary metabolite O-desmethyltramadol after oral administration of 100 mg tramadol on Day 7 of pretreatment with oral placebo, celecoxib (200 mg twice daily) or etoricoxib (120 mg once daily) in 12 healthy volunteers.

						Geometric mean ratio (90% CI)	
Variable	**Placebo**	**Celecoxib**	***p***	**Etoricoxib**	***p***	**Celecoxib/ placebo**	**Etoricoxib/ placebo**
Tramadol							
$AUC_{0-\infty}$ (ng·h/mL)	2354.2 (969.0)	2600.0 (797.5)	0.765	2396.7 (840.1)	0.992	1.13 (1.06–1.21)	1.04 (0.95–1.15)
C_{max} (ng/mL)	283.2 (89.0)	297.1 (62.8)	0.862	263.2 (69.7)	0.845	1.08 (0.99–1.18)	0.95 (0.86–1.04)
$t_{1/2}$ (h)	5.0 (1.0)	5.3 (1.2)	0.804	5.3 (1.2)	0.836	1.06 (1.01–1.12)	1.06 (1.02–1.10)
t_{max} (h)	2 (1–4)	2 (1–3)	0.591	3 (1.5–4)	0.126		
CL/F (L/min)	0.83 (0.36)	0.72 (0.29)	0.006	0.77 (0.24)	0.836	0.88 (0.83–0.94)	0.96 (0.87–1.06)
V_z/F (L)	339.2 (102.7)	312.6 (76.7)	0.636	338.1 (72.8)	0.989	0.94 (0.86–1.03)	1.02 (0.93–1.11)
O-desmethyltramadol							
$AUC_{0-\infty}$ (ng·h/mL)	701.4 (206.1)	607.7 (170.3)	0.001	686.5 (259.6)	0.982	0.86 (0.81–0.92)	0.96 (0.90–1.03)
C_{max} (ng/mL)	62.8 (19.5)	47.1 (15.2)	<0.001	52.9 (16.7)	0.001	0.75 (0.71–0.78)	0.84 (0.79–0.90)
$t_{1/2}$ (h)	5.6 (1.1)	6.1 (1.3)	0.69	2.6 (0.7)	0.809	1.08 (1.03–1.14)	1.06 (0.99–1.14)
t_{max} (h)	2 (1–5)	2.5 (1–6)	0.326	3 (2–6)	0.035		
AUC_m/AUC_p	0.33 (0.12)	0.25 (0.08)	<0.001	0.30 (0.09)	0.130	0.76 (0.69–0.84)	0.92 (0.84–1.02)

Note: Data are shown as arithmetic mean (SD) and as the geometric mean ratios with the 90% confidence interval (CI) in parenthesis, except for t_{max}, which is given as median and range.
Abbreviations: $AUC_{0-\infty}$, area under plasma concentration–time curve extrapolated to infinity; AUC_m/AUC_p, $AUC_{0-\infty}$ of O-desmethyltramadol/$AUC_{0-\infty}$ of tramadol; CL/F, apparent oral clearance; C_{max}, peak plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, time to peak concentration; V_z/F, apparent volume of distribution.

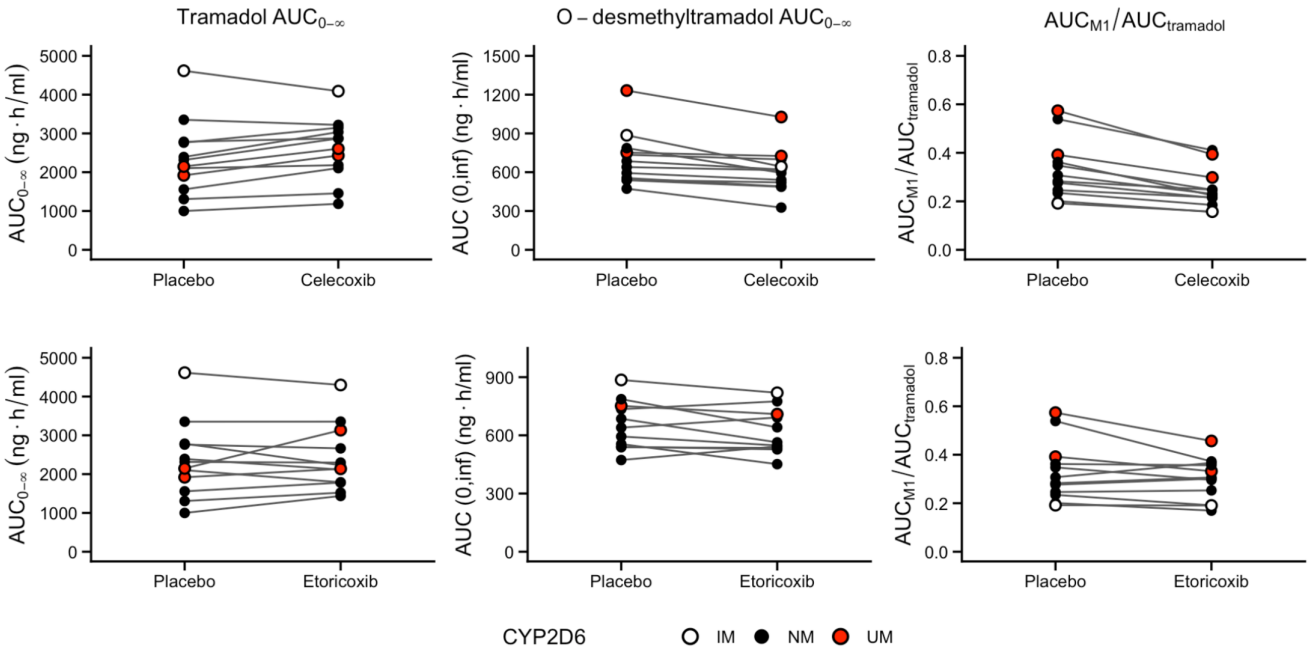

FIGURE 2 | Individual values of the area under plasma concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$) for tramadol and O-desmethyltramadol and the O-desmethyltramadol to tramadol ratio after 100 mg oral tramadol following 8-day pretreatment with celecoxib (200 mg twice daily, top panel) or etoricoxib (120 mg once daily, lower panel), compared with placebo in 12 healthy volunteers. Colouring of the symbols denote CYP2D6 phenotypes (normal, intermediate, ultrarapid metabolisers).

Pharmacological effects showed the expected temporal patterns following tramadol administration across all treatment conditions (Figure 3). When summarised as area under the effect–time curve from 0 to 12 h ($AUEC_{0–12}$), neither celecoxib nor etoricoxib pretreatment produced statistically or clinically meaningful changes in subjective drug effect, psychomotor performance (DSST) or experimental cold pain measures (CPT, CPI30 and CPI60) compared with placebo (Table 2). Point estimates for treatment effects were close to unity or zero across endpoints, and CI were wide, reflecting interindividual variability and the limited sample size. Overall, the findings in pharmacological effects indicate that the modest pharmacokinetic changes observed with celecoxib pretreatment were not associated with detectable alterations in analgesic or central nervous system effects.

4 | Discussion

In this randomised crossover study in healthy volunteers, pretreatment with celecoxib resulted in modest but statistically significant alterations in the pharmacokinetics of tramadol and its active metabolite O-desmethyltramadol, whereas etoricoxib had minimal and non-significant effects. These pharmacokinetic changes were not associated with clinically meaningful differences in pharmacological effects responses or occurrence of

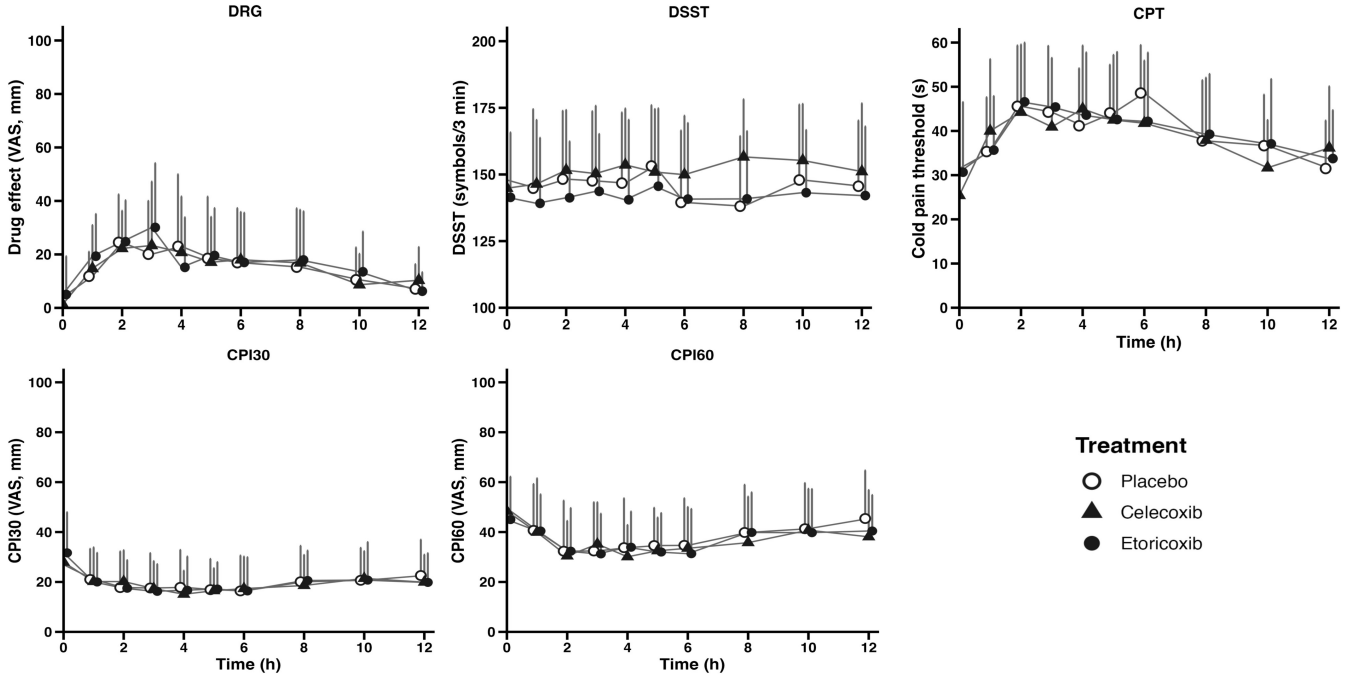

FIGURE 3 | Time courses of responses in pharmacological effects following 8-day pretreatment with celecoxib (200 mg twice daily) or etoricoxib (120 mg once daily), compared with placebo in 12 healthy volunteers. Panels show subjective drug effect (DRG), digit symbol substitution test (DSST), cold pain threshold (CPT) and cold pain intensity at 30 (CPI30) and 60 s (CPI60). VAS, visual analogue scale. Data are presented as mean (SD [$n = 12$]). Higher values indicate stronger drug effect, improved psychomotor performance and greater cold pain tolerance, whereas lower values indicate reduced pain intensity.

TABLE 2 | Pharmacological effects exposure ($AUEC_{0–12}$) of experimental pain and psychomotor endpoints after oral administration of 100 mg tramadol on Day 7 of pretreatment with oral placebo, celecoxib (200 mg twice daily) or etoricoxib (120 mg once daily) in 12 healthy volunteers.

						Geometric mean ratio (90% CI)	
Variable	**AUEC placebo**	**AUEC celecoxib**	***p***	**AUEC etoricoxib**	***p***	**Celecoxib/ placebo**	**Etoricoxib/ placebo**
Drug effect (VAS, mm)	183.9 (172.7)	187.2 (161.4)	0.993	206.0 (156.6)	0.829	3.29 (−87.89, 94.47)	22.13 (−69.06, 113.31)
DSST (symbols/3 min)	1741.4 (304.7)	1824.9 (259.0)	0.118	1702.1 (286.8)	0.666	1.05 (1.00, 1.11)	0.98 (0.93, 1.03)
CPT (s)	479.4 (120.8)	463.3 (136.3)	0.765	478.8 (120.7)	0.998	0.95 (0.82, 1.12)	1.00 (0.85, 1.17)
CPI30 (VAS, mm)	233.2 (156.0)	229.1 (127.6)	0.841	230.5 (141.6)	0.933	1.05 (0.86, 1.26)	1.03 (0.85, 1.24)
CPI60 (VAS, mm)	458.2 (212.6)	433.6 (189.9)	0.892	439.0 (166.8)	0.98	0.96 (0.78, 1.18)	0.99 (0.80, 1.21)

Abbreviations: $AUEC_{0–12}$, area under the effect–time curve from 0 to 12 h, calculated by the linear trapezoidal rule; CI, confidence interval; CPI, cold pain intensity at 30 s (CPI30) and 60 s (CPI60); CPT, cold pain threshold; DSST, digit symbol substitution test; VAS, visual analogue scale.

adverse effects by tramadol. The study design did not include a COX-2 inhibitor-only arm. However, the crossover design allows each subject to serve as their own control, and pharmacological endpoints were assessed following tramadol administration under each pretreatment condition. The objective was to evaluate whether pretreatment modifies tramadol effects, rather than to quantify the independent analgesic effects of COX-2 inhibitors.

Celecoxib pretreatment modestly increased tramadol exposure and reduced O-desmethyltramadol formation, findings consistent with weak inhibition of CYP2D6-mediated O-demethylation [27]. However, the magnitude of these effects was small compared with those observed with strong CYP2D6 inhibitors. In our previous interaction study with terbinafine, tramadol exposure increased more than twofold, and O-desmethyltramadol exposure was markedly reduced, clearly demonstrating a clinically relevant interaction [24]. Notably, the magnitude of the celecoxib effect on tramadol bioactivation appears smaller than that reported for the CYP2D6 probe substrates dextromethorphan and metoprolol, which is consistent with substrate-dependent variability in CYP2D6-mediated DDIs [9]. Tramadol bioactivation depends on CYP2D6 but also involves parallel metabolic pathways [5, 6] and pharmacodynamic contributions from the parent compound, which may attenuate the apparent impact of weak CYP2D6 inhibition. In contrast, the changes observed with celecoxib in the present study were largely within bioequivalence limits and are unlikely to be clinically important. Etoricoxib did not meaningfully affect tramadol or O-desmethyltramadol pharmacokinetics, consistent with its lack of documented CYP2D6 inhibition.

Tramadol to O-desmethyltramadol AUC ratio provides an integrated measure of CYP2D6-dependent bioactivation. Celecoxib pretreatment resulted in a statistically significant reduction in this ratio, indicating decreased relative formation of the active metabolite. This finding is consistent with weak inhibition of CYP2D6-mediated O-demethylation. However, the magnitude of the effect was modest compared with that observed with strong CYP2D6 inhibitors and was not accompanied by measurable changes in pharmacological effects endpoints. In contrast, etoricoxib did not significantly affect the AUC ratio, supporting the absence of a relevant interaction at the level of tramadol bioactivation.

These findings are consistent with previous findings on tramadol DDIs. Potent enzyme induction with rifampicin markedly decreased tramadol and O-desmethyltramadol exposure after both oral and intravenous administration [28], whereas strong CYP2D6 inhibition with terbinafine produced a pronounced shift from active metabolite formation towards parent tramadol exposure [24]. In contrast, itraconazole had no meaningful effect in subjects with functional CYP2D6 activity [24]. Ticlopidine increased tramadol exposure and inhibited O-demethylation, illustrating that clinically relevant shifts may also occur through combined metabolic and clearance mechanisms [29]. The modest changes observed with celecoxib in the present study are consistent with a weak inhibitory effect and appear unlikely to be clinically important in individuals with normal CYP2D6 activity.

The absence of differences in pharmacological effects despite modest pharmacokinetic changes is consistent with current understanding of tramadol pharmacology. Although O-desmethyltramadol contributes to μ-opioid receptor activation, small changes in O-desmethyltramadol exposure within the observed range may not translate into detectable differences in analgesic or central nervous system effects, particularly in healthy volunteers [10, 11]. In chronic administration of tramadol, there is an increased risk of serotonergic adverse effects, such as gastrointestinal bleeding [30, 31], and this may be a clinical risk factor when parent tramadol exposure is increased. Although the present data suggest little interaction risk in normal metabolisers, patients with reduced CYP2D6 activity (genotype or phenoconversion due to strong CYP2D6 inhibitors) may have less margin for additional pathway perturbations.

Recent clinical pharmacogenetic and DDI literature has emphasised that CYP2D6-dependent tramadol metabolism is strongly influenced not only by genotype but also by pharmacological inhibition, resulting in phenoconversion and reduced formation of the active metabolite O-desmethyltramadol, with potential clinical consequences for analgesic efficacy [8, 9, 32, 33]. However, the modest pharmacokinetic changes observed with celecoxib in the present study appear insufficient to produce such clinically relevant phenoconversion effects.

CYP2D6 genotype distribution in this study was dominated by normal metabolisers, with limited representation of intermediate and ultrarapid metabolisers. Although CYP2D6 genetic variability is known to influence tramadol metabolism and response, the present study was not powered to evaluate genotype-dependent effects or gene–drug–drug interactions. The pharmacokinetic findings therefore primarily reflect individuals with normal CYP2D6 activity, and the limited number of intermediate and ultrarapid metabolisers precludes reliable subgroup analyses. Any exploratory stratification would have yielded imprecise and potentially misleading estimates. Larger studies would be required to evaluate potential gene–drug–drug interactions involving tramadol and CYP2D6 inhibitors.

In conclusion, celecoxib produces modest alterations in tramadol and O-desmethyltramadol pharmacokinetics consistent with weak CYP2D6 inhibition, whereas etoricoxib has minimal effects. These pharmacokinetic changes do not translate into clinically meaningful differences in pharmacological effects. The findings suggest that co-administration of tramadol with celecoxib or etoricoxib is unlikely to result in clinically relevant DDIs in individuals with normal CYP2D6 activity.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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