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THE EFFECT OF SINGLE-DOSE TRAMADOL ON OXYCODONE CLEARANCE

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□ **Abstract—We have noticed increased prescribing of tramadol by emergency physicians for breakthrough pain in patients chronically taking oxycodone. Both oxycodone and tramadol undergo oxidative metabolism by CYP2D6 and CYP3A4, suggesting the possibility that tramadol may compete with oxycodone for metabolism. A randomized controlled trial in 10 human volunteers was performed to determine if single-dose tramadol therapy would impair oxycodone clearance. Subjects were randomized whether to enter the control or experimental arm of the study first, with each subject serving as his or her own control. In the control arm, each subject received 10 mg immediate-release oxycodone orally and had serial plasma oxycodone and oxymorphone concentrations measured over 8 h. The experimental arm was identical except that 100 mg tramadol was ingested 1.5 h before oxycodone. Clearance divided by fraction absorbed (CL/f) was calculated using the dose and the area under the 8-h time-plasma oxycodone concentration curve. Peak plasma oxycodone concentrations (C_{max}) and time until peak oxycodone concentrations (T_{max}) were secondary outcome parameters. Group size was chosen to produce a power of 0.8 to detect a 20% difference in CL/f between study arms. Values for CL/f, C_{max}, and T_{max} were compared between study arms using two-tailed, paired *t*-tests. No statistically significant difference between groups was demonstrated for any parameter. We failed to demonstrate that single doses of tramadol impaired oxycodone clearance.** © 2007 Elsevier Inc.

□ **Keywords—tramadol; oxycodone; drug interaction; pharmacokinetics; CYP2D6; CYP3A4**

INTRODUCTION

Oxycodone is a commonly used opiate analgesic for moderate to severe pain that acts by activating *mu* opiate receptors. Only about 8–14% of oxycodone is excreted in the urine as unchanged drug. The majority of parent compound is metabolized by cytochrome P450 3A4 (CYP3A4) to noroxycodone, a relatively inactive metabolite, before urinary excretion (1–3). About 10% of oxycodone undergoes metabolism by cytochrome P450 2D6 (CYP2D6) to oxymorphone, an active metabolite that is much more potent than oxycodone, but frequently present in concentrations too low to contribute to analgesia (1–3).

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Tramadol is an oral analgesic also used for moderate to severe pain. Analgesic activity is thought to result from a combination of norepinephrine uptake inhibition and *mu* opiate receptor activation (4). Tramadol undergoes metabolism by CYP3A4 to form N-desmethyltramadol, and by CYP2D6 to form O-desmethyltramadol, an active metabolite that displays higher affinity for *mu* receptors than the parent drug (4,5).

We have increasingly observed emergency physicians as well as primary care physicians and pain specialists to prescribe intermittent tramadol doses for breakthrough pain in patients chronically taking oxycodone. These physicians choose tramadol over additional opiates due to less respiratory depression and an alternative mechanism of analgesia (inhibition of norepinephrine uptake) (4).

Because both tramadol and oxycodone undergo metabolism by CYP3A4 and CYP2D6, it was speculated that tramadol might impair clearance of oxycodone due to competition for the active site on these enzymes. A randomized controlled trial was conducted using healthy volunteers to determine if oxycodone clearance was affected by single doses of tramadol.

MATERIALS AND METHODS

A randomized, controlled trial was performed in human volunteers in which each subject served as his or her own control. Study approval was obtained from Banner Good Samaritan Medical Center Institutional Review Board. Written informed consent was obtained from healthy men and women between the ages of 18 and 40 years and within 20% ideal body weight who had taken no prescription or over-the-counter medications other than oral contraceptives within the last 6 weeks. A physical examination was performed on all subjects, and all women underwent testing to exclude pregnancy.

CYP2D6 expression is polymorphic, and because CYP2D6 poor metabolizers would be unexpected to experience a further decline in oxidative drug metabolism in the face of an inhibitor, all subjects were genotyped for CYP2D6 activity. Exclusion criteria comprised 1) slow CYP2D6 metabolizer genotype; 2) known hypersensitivity to tramadol, oxycodone, or related opioid analgesics; 3) history of a seizure disorder; 5) major medical illness; 6) pregnancy; or 7) participation in a research trial within the last 6 months.

Subjects were randomized by blindly drawing a number from an envelope to enter either a control or experimental arm of the study first. In the control arm, subjects ingested nothing but water by mouth after midnight the previous evening. On the morning of the study, a peripheral intravenous catheter was placed and kept patent with a normal saline flush. Ten mg of immediate-release oxycodone (tablet) was taken orally followed by several swallows of water at 9:00 a.m. Blood was drawn at times 0.3, 0.6, 1, 2, 5 and 8 h after ingestion of oxycodone into sodium EDTA Vacutainer® (BD, Franklin Lakes, NJ) tubes for measurement of plasma oxycodone and oxymorphone concentrations. Blood samples underwent immediate centrifugation, and separated plasma was frozen for batch analysis. Food intake was allowed beginning 2 h after oxycodone ingestion.

The procedure was identical in the experimental arm of the study except that 100 mg tramadol (capsule) was taken by mouth at 7:30 a.m., 90 min before the ingestion of oxycodone. Each subject completed the alternative arm of the study between 2 and 6 weeks after the initial arm. Women taking oral contraceptives were taking identical preparations during both arms of the study.

Plasma oxycodone and oxymorphone concentrations were measured by gas chromatography-mass spectrometry. This method had a limit of quantification of 1 μg/L. Within-run and between-runs coefficients of variation for oxycodone were 3.9% and 4.2%, respectively; and for oxymorphone were 5.3% and 6.2%, respectively.

CYP2D6 poor metabolizers have either two copies of non-functional alleles or deletion of the CYP2D6 gene. If patients were homozygous or compound heterozygous for any combination of the alleles CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, and CYP2D6*7, they were considered genotypically poor metabolizers. Genotyping to determine poor-metabolizer status included testing for CYP2D6*3, CYP2D6*4, CYP2D6*6, and CYP2D6*7 using allele-specific PCR (polymerase chain reaction) as previously described by Chen and Wedlund (6). The relatively uncommon CYP2D6*6 or CYP2D6*7 alleles were only evaluated on those samples that were heterozygous for CYP2D6*3, CYP2D6*4, and CYP2D6*5 alleles. The presence of gene duplication or deletion was also detected using allele-specific PCR as previously described (7–11). Positive and negative controls were included with each analysis. PCR products were resolved using submarine agarose gel electrophoresis and visualized using ethidium bromide staining and ultraviolet light. Final genotype results were released by a board-certified clinical chemist.

The primary outcome parameter for this study was oxycodone clearance. Area under the plasma oxycodone concentration time curve (AUC) from 0 to 8 h was calculated using the trapezoidal method, and CL/f (clearance/fraction absorbed) was calculated from dose divided by the AUC (12). The values for CL/f were compared between study arms using a paired *t*-test. Maximal plasma oxycodone concentrations (C_{max}) and time until maximal concentrations (T_{max}) were also compared between arms with a paired *t*-test. A two-tailed *p* value of < 0.05 was considered significant.

Mandema and colleagues' report of CL/f values measured over 8 h after ingestion of oxycodone provided values used for group-size calculations (13). We considered a decline of oxycodone CL/f of 20% to be clinically significant, and using a two-tailed alpha of 0.05, 10 subjects were required to achieve 80% power to detect this difference. Anticipating the possibility of dropouts, 12 subjects were enrolled.

RESULTS

Results are summarized in Table 1. Seven men and three women completed the study. One woman dropped out due to development of unrelated illness before completion of the study; her results are neither shown nor included in statistical analyses. One man chose to drop out after giving consent, but before receiving any medication. No subject was a CYP2D6 slow metabolizer. Subjects 5 and 9 were intermediate metabolizers (CYP2D6 *1/*4) and subject 7 was an ultra-rapid metabolizer (CYP2D6 *1/dup). The remaining subjects were extensive metabolizers (CYP2D6 *1/*1).

Differences (tramadol arm parameter minus control arm parameter) between study arms for CL/f (mean difference -12.1 L · hr^{-1} f^{-1}; 95% confidence interval [CI] -27.6 to 3.8; $p = .12$), C_{max} (mean difference 1.1 μg/L; 95% CI -7.1 to 9.3; $p \geq 0.7$) and T_{max} (mean difference -0.3 h; 95% CI -1.27 to 0.67; $p = 0.5$) did not reach statistical significance.

Plasma oxymorphone concentrations were < 1 μg/L in all samples.

DISCUSSION

Oxycodone has an oral bioavailability of about 60%. After ingestion of immediate-release preparations, oxycodone is rapidly absorbed to produce peak plasma levels in an average of 1.6 h and then eliminated with a half-life of 3 to 5.7 h (1,2,14). Peak oxycodone concentrations ranging from 13 to 46 μg/L were found in 12 patients who received 10 mg oral oxycodone (14). The majority of oxycodone undergoes metabolism by CYP3A4 to noroxycodone before urinary excretion. About 10% of oxycodone undergoes metabolism by CYP2D6 to form oxymorphone, an active metabolite that is much more potent than oxycodone, but present in concentrations too low to contribute to oxycodone's analgesia after typical doses (1,2).

Tramadol is rapidly absorbed with a bioavailability of about 70% after single doses (4). After ingestion of a typical

Table 1. Summary of Demographics and Results for Each of 10 Subjects

Subject #	Age Difference, Years	Gender	Weight Kg	CYP2D6 Genotype	Treatment	C_{max} μg/L	T_{max} h	CL/f L · hr^{-1} f^{-1}	Cl/f Difference L · hr^{-1} f^{-1}
1	29	Male	65.9	*1/*1	Control	11.4	1	196.2	
					Tramadol	11	1	214.0	17.8
2	30	Male	79.5	*1/*1	Control	15	1	172.7	
					Tramadol	14.8	1	119.0	−53.7
3	29	Female	54.5	*1/*1	Control	15.3	5	127.5	
					Tramadol	24.8	1	95.5	−32
4	30	Male	61.4	*1/*1	Control	29.6	0.6	107.4	
					Tramadol	31.5	0.6	86.0	−21.4
5	34	Male	106.8	*1/*4	Control	33.8	0.6	125.8	
					Tramadol	41.3	0.6	104.5	−21.3
6	37	Female	59.1	*1/*1	Control	33.5	1	93.0	
					Tramadol	56.4	0.6	73.8	−19.2
7	30	Female	72.7	*1/dup	Control	36.9	0.6	91.2	
					Tramadol	15	1	102.0	10.8
8	19	Male	68.2	*1/*1	Control	16	1	143.1	
					Tramadol	16.4	1	143.6	0.5
9	31	Male	70.0	*1/*4	Control	23.5	1	105.0	
					Tramadol	17	2	107.5	2.5
10	18	Male	88.6	*1/*1	Control	18	0.6	210.3	
					Tramadol	15.7	0.6	211.0	0.7

CYP2D6 genotypes were as follows: *1/*1, extensive metabolizer; *1/dup, ultrarapid metabolizer; *1/*4, intermediate metabolizer. Each subject swallowed a 10-mg immediate-release oxycodone tablet, alone (control arm), or swallowed 10-mg immediate-release oxycodone preceded by 100 mg tramadol 90 min earlier (tramadol arm). Differences (tramadol arm parameter minus control arm parameter) in values for oxycodone clearance (CL/f), maximal plasma oxycodone concentration (C_{max}), and time after ingestion C_{max} was achieved (T_{max}) did not reach statistical significance with two-tailed, paired *t*-tests: CL/f mean difference = -12.1 L · hr^{-1} f^{-1} (95% confidence interval [CI] -27.6 to 3.8; $p = 0.12$); C_{max} mean difference = 1.1 μg/L (95% CI -7.1 to 9.3; $p \geq 0.7$); T_{max} mean difference = -0.3 h (95% CI -1.27 to 0.67; $p = 0.5$).

100-mg dose, peak plasma tramadol levels are reached in about 1.6 h, and tramadol is eliminated with a half-life of about 5.6 h (4). Tramadol undergoes *N*-demethylation by CYP3A4 to form *N*-desmethyltramadol. CYP2D6 demethylates at the *O* position to produce *O*-desmethyltramadol—an active metabolite having a higher affinity for *mu* receptors than the parent drug (5).

The ability of tramadol to impair oxycodone clearance was examined because both drugs are metabolized by CYP2D6 and CYP3A4. We were unaware of any studies suggesting that tramadol affected CYP2D6 or CYP3A4 transcription, translation, or degradation half-life. Rather, our concern was for competitive inhibition of oxidative metabolism, the basis for most drug-drug interactions in which one drug impairs the clearance of another.

Authors have cautioned that co-ingestion of fluoxetine, a CYP2D6 inhibitor, might impair oxycodone clearance (3,15). However, these cautions seem to be based to a large extent on in vitro studies demonstrating that fluoxetine inhibits CYP2D6 conversion of oxycodone to oxymorphone in hepatic microsomes, or to an autopsy series in which some subjects who were suspected to have died from oxycodone toxicity were found to be slow CYP2D6 metabolizers (16,17). Given the small contribution that metabolism by CYP2D6 makes to total oxycodone clearance, and a compensatory increase in oxidation by CYP3A4 in the face of CYP2D6 inhibition, it was not expected that CYP2D6 inhibition would necessarily meaningfully impair oxycodone clearance (2).

Heiskanen and colleagues reported that coadministration of 20 mg controlled-release oxycodone with quinidine, an inhibitor of CYP2D6 and CYP3A4, increased the 24-h AUC for plasma oxycodone over that when taking oxycodone alone (2). However, the difference did not reach statistical significance. Although Heiskanen also reported higher maximal plasma oxycodone levels with co-administration of quinidine, the absolute difference in mean values was only 2.3 μg/L, probably of little clinical consequence.

Our subjects achieved values for CL/f, C_{max} and T_{max} similar to those previously reported (13,14). However, in this randomized, controlled trial, a statistically significant difference in oxycodone clearance was not demonstrated when single doses of tramadol preceded the ingestion of oxycodone. Tramadol's rapid absorption and elimination half-life of about 5.6 h should have maintained therapeutic plasma concentrations during most, if not all, of the time plasma oxycodone concentrations were measured. Because oxycodone's metabolism by CYP3A4 occurs in gut epithelium and liver during absorption, tramadol's ability to affect oxycodone metabolism was optimized by administering it before oxycodone. Despite such optimization, we could detect no statistically significant differences in peak plasma oxycodone concentrations or oxycodone clearance.

Single oral doses of oxycodone produce circulating oxymorphone concentrations well below 2 μg/L (1). Oxymorphone was not detected in any plasma sample using a quantification limit of 1 μg/L.

Given that all but three subjects were extensive metabolizers, it would be inappropriate to consider a post hoc subgroup statistical analysis based on CYP2D6 genotype. It is interesting to note, however, that subject 7, an ultra-rapid metabolizer, demonstrated an increase in oxycodone clearance with tramadol. This is the opposite of what would be expected if tramadol was an important inhibitor of CYP2D6.

A limitation to this study is that group size calculations were designed to detect a reduction of oxycodone clearance of 20%, which was considered clinically significant. Statistically significant smaller reductions in clearance might be detected with a larger study population.

Subjects in this study received single doses of tramadol because we were interested in the use of intermittent doses of tramadol for breakthrough pain in patients chronically ingesting oxycodone. Repeated doses of tramadol given every 6 h would have resulted in higher steady-state plasma tramadol concentrations, possibly engendering a greater competitive advantage for metabolism by CYP2D6 and CYP3A4. However, clinical trials have not reported tramadol to be an important inhibitor of CYP450 when given with other agents. Furthermore, maximal plasma tramadol concentrations are only 16% higher when taking 100 mg four times daily than when taking 100 mg as a single dose, a rather minor difference (4).

The purpose of our study was neither to examine pharmacodynamic interactions (e.g., analgesia, sedation, respiratory depression) between tramadol and oxycodone nor to determine if oxycodone impaired tramadol clearance. Thus, no comment can be made regarding these issues.

A randomized controlled trial has failed to demonstrate that single doses of tramadol reduce oxycodone clearance.

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