Effects of an Opioid (Oxycodone/Paracetamol) and an NSAID (Bromfenac) on Driving Ability, Memory Functioning, Psychomotor Performance, Pupil Size, and Mood

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Objective: It has been suggested that driving a car is relatively safe when the driver is treated with nonsteroid anti-inflammatory drugs than when he or she is treated with opioid analgesics. However, the evidence for this statement is scarce. The objective of this study was to determine the effects of a nonsteroid anti-inflammatory drug (bromfenac 25 mg and 50 mg) and an opioid (oxycodone/paracetamol 5/325 mg and 10/650 mg), and placebo on driving ability, memory functioning, psychomotor performance, pupil size, and mood.

Methods: Out of 30 healthy volunteers, 18 completed this randomized, double-blind, placebo-controlled crossover study, before the study had to be stopped due to bromfenac being pulled out from the market. One hour after administration of the drugs, the participants performed a standardized driving test during normal traffic. Thereafter, driving quality, mental effort and mental activation during driving were assessed. A laboratory test battery was performed 2.5 hours after administration of the drug. Visual analog scales assessing mood and pupil measurements were performed on several occasions during each test day.

Results: Both analgesics did not significantly affect performance in any test. However, volunteers reported that significantly more effort was needed to perform the driving test when treated with oxycodone/paracetamol, and that they experienced increased sedation and reduced alertness. Also, the pupil size was significantly decreased. In contrast, subjective assessments after both doses of bromfenac matched that of placebo.

Discussion: No significant impairment in behavior was found in the volunteers for both bromfenac and oxycodone/paracetamol. The lack of impairment from oxycodone/paracetamol may have been related to the participants reporting increased effort during driving while under the influence of this drug.

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The majority of patients treated with analgesics are ambulatory outpatients. Because driving is critical to maintaining independence in today's society, it is reasonable to assume that these patients are also involved in potentially dangerous daily activities such as driving a car. Pain is usually managed by pharmacological treatment with opioids or nonsteroid anti-inflammatory drugs (NSAIDs). Unfortunately, the effects of these analgesics on driving ability and consequent safety are not well understood.

This becomes evident from the conflicting results from epidemiological studies. In these studies, the risk of becoming involved in a traffic accident when treated with analgesics is expressed as an odds ratio (OR) with an accompanying 95% confidence interval (CI) that must be above 1.0 to produce a statistically significant value. Ray and colleagues[1] examined the traffic accident risk in elderly drivers treated with psychoactive drugs. The use of opioid analgesics did not significantly increase traffic accident risk (OR = 1.1; 95%CI = 0.5–2.4). In contrast, Leveille and colleagues,[2] who also examined traffic accident risk in the elderly treated with psychotropic drugs, did report an increased traffic accident risk for patients using opioid analgesics (OR = 1.8; 95%CI = 1.0–3.4), including codeine-containing opioids, propoxyphene, and oxycodone. McGwin and colleagues[3] reported an increased traffic accident risk in the elderly using NSAIDs (OR = 1.7; 95%CI = 1.0–2.6). In these cohort studies in the elderly it remains unclear whether analgesics, pain, the underlying disease process, or a combination of these factors caused the accidents. Thus, although the use of both opioids and NSAIDs has been associated with increased traffic accident risk in the elderly, current evidence is limited and further epidemiological research is necessary.

Opioid labeling often warns of drowsiness and sedation in the users , and danger in their operating heavy machinery. However, reviews of experimental research on behavioral effects of opioids conclude that these analgesics have little to no effect on driving related skills

measured in a number of psychomotor tests in the laboratory.[4–6] Also, a driving simulator study showed no significant impairment in people on stable dosages of oral opioids.[7] Up to now, effects of commonly used analgesics on driving ability have not been determined by means of standardized driving tests during normal traffic. Because opioids predominantly act centrally (on the central nervous system), whereas NSAIDs reduce pain predominantly by peripheral mechanisms (at the site of injury), it can be expected that compounds from these drug classes may differentially affect driving ability.

The present study compares the effects on the driving ability and cognitive functioning of people who are on NSAID (bromfenac) and an opioid analgesic (oxycodone/paracetamol). Oxycodone is a full μ-opioid agonist that is frequently prescribed in combination with paracetamol. This combination is used to reduce the opioid dosage while retaining the analgesic efficacy, to reduce opioid-related adverse effects. In this context, it is important to note that paracetamol itself has been shown to produce neither significant subjective effects,[8] nor significant performance impairments on a variety of cognitive and psychomotor tests.[9] The recommended dose is 5 mg oxycodone with 325 mg paracetamol. Bromfenac, with a recommended dose of 25 mg, is an NSAID indicated for the short-term management (< 10 days) of acute pain. Taking the differences between both types of analgesics into account, it is hypothesized that oxycodone/paracetamol will significantly impair driving performance, whereas driving is not expected to be significantly affected after bromfenac. To gain supportive evidence, laboratory tests measuring driving related skills, subjective assessments, and pupil measurements were conducted.

METHODS

Participants

Thirty healthy volunteers were enrolled to participate in the study. The Medical Ethical Committee of the University Medical Center, Utrecht, approved the study and participants were treated according to ICH guidelines for Good Clinical Practice and the Declaration of Helsinki and its amendments. Written informed consent was obtained before their inclusion in the study. Participants underwent a detailed medical examination and their medical history was screened. Before the start and at the end of the study, blood chemistry, hematology and urinalysis were determined. During screening, a 12-lead ECG was recorded. To confirm compliance, participants were tested for the presence of alcohol and drugs of abuse (amphetamines, barbiturates, cannabinoids, benzodiazepines, cocaine and opioids) on all test days and a physical examination was conducted. In addition, female participants underwent a β-HCG pregnancy test. The examination and tests were conducted before treatment administration. Participants were intensively trained to perform the tests before taking part in the study. Training was stopped when participants failed to show any improvement in particular tests on at least 3 consecutive trials (ie, baseline performance).

Procedure

In a double-blind crossover design, bromfenac 25 mg, bromfenac 50 mg, oxycodone/paracetamol 5/325 mg, oxycodone/paracetamol 10/650 mg, and placebo were administrated in identically appearing capsules with 200-mL tap water, exactly 30 minutes before a standardized breakfast. Treatment sequences were randomized across the participants. One hour after treatment administration, a standardized driving test was administered. Approximately 2.5 hours after intake a laboratory test battery was performed including a Sternberg memory scanning test, tracking test, and divided attention test. Test days were separated by a washout period of 7 days (range from 4 to 14 days).

The Driving Test

The standardized 100-km driving test[10] was performed during normal traffic over a 50-km segment of the primary highway running between 2 Dutch cities, Utrecht (start and end point) and Arnhem (turning point). The highway consists of 2 traffic lanes in both directions. Participants were instructed to drive with a steady lateral position within the right (slower) traffic lane, while maintaining a constant speed of 90 km/h (56 miles/h). Participants were allowed to deviate from the instructions to overtake a slower-moving vehicle in the same traffic lane. A licensed driving instructor who had access to dual controls sat in the right front seat, guarding the participants safety during the driving test. Driving tests could be terminated before completion if the driving instructor or the participants felt it was unsafe to continue. The amount of weaving of the car, measured by the standard deviation of the lateral position (SDLP, cm), is an index of driving safety, and the primary outcome parameter of the driving test. SDLP expresses vehicle control in terms of how well participants are able to maintain their chosen lateral position within the right traffic lane. The standard deviation of speed (km/h) is a secondary parameter, showing how well participants are capable of maintaining a constant speed. Mean lateral position and speed are control variables, determined to ensure that participants performed the tests according to the instructions. Data were recorded continuously during the test, and edited off-line to remove data that were disturbed by extraneous events (eg, overtaking maneuvers, traffic jams, windblasts). Time-on-task of the driving test is approximately 75 minutes.

Laboratory Tests

Sternberg Memory Scanning Test

After learning a memory set of 1 to 5 digits (0–9), a single digit (or probe) was presented. Participants were instructed to indicate by button-press whether the probe stimulus was part of the memory set (right hand button) or not (left hand button). A total of 100 different memory sets were presented. Parameters of the test were reaction

time (ms) and percentage errors. Total time-on-task was approximately 13 minutes.

Tracking Test

Participants were instructed to keep an unstable moving bar in the middle of a horizontal plane (14-cm wide). They could counteract or reverse the movements of the unstable bar with the aid of a computer-mouse. If the bar hit the edge of the plane, the participants had to start again. The Root Mean Square of the tracking error (RMS) was the outcome measure of the tracking test. An easy and hard version of the tracking test was included. Total time-on-task was approximately 8 minutes.

Divided Attention Test

The divided attention test is a combination of 2 tests performed with both hands simultaneously. With the right hand, participants performed the easy version of the tracking test, as described above. RMS was the outcome measure. Concurrently, a Sternberg memory scanning test (fixed version) was performed with the left hand. Before the start, a memory set of 4 digits was presented. Thereafter, subsequent digits were presented on the computer screen. By button-press, participants had to indicate whether a digit was part of the learned memory set (right button) or not (left button). The mean reaction time (ms) was the parameter of interest. The duration of the test was approximately 9 minutes.

Pupil Measurements

Pupil measurements were performed during the test days to ensure than subjects were sensitive to opioid-induced effects. All measurements were performed in a soundproof test room with standard dimly light conditions. Subjects' head position was fixed at 80 cm from an infrared E4000 Eye View Monitor. The horizontal pupil diameter (mm) was continuously recorded with a frequency of 60 Hz. Measurements were performed 5 minutes (T1), 25 minutes (T2), 40 minutes (T3), 145 minutes (T4), and 220 minutes (T5) after treatment administration. The pupil diameter was the mean of 2 subsequent 1-minute measurements, separated by 1 resting minute. At T4, 3 subsequent 1-minute measurements were made. Blinks were defined as eye closures of 40 to 340 ms, including a maximal closure onset of 40 ms and opening onset of 100 ms. Blinks (40 to 340 ms), eye closures (> 340 ms), artifacts (< 40 ms), and hippus were removed from the data before calculating the mean pupil diameter.

Subjective Assessments

Before and after the driving test, participants rated their alertness on a 21-point equal interval scale. After the driving test, participants indicated the perceived quality of their driving performance on a visual analog scale, which ranged from "I drove exceptionally badly" to "I drove exceptionally well" around a midpoint of "I drove normally". The level of effort they had to invest in performing the task was indicated on a 15-cm scale, which ranged from "absolutely no effort" to "extreme effort". The scale included consecutive sublevels indicating "almost no effort", "a little effort", "some effort", "rather much effort", "considerable effort", "great effort", and "very great effort".

Addiction Research Center Inventory (ARCI)-49 Questionnaire

After the driving test the addiction research center inventory (ARCI)-49 questionnaire was completed. The ARCI-49 is a short version of the ARCI comprising 49 yes/no questions that relate to 5 scales, differentiating between mood changes induced by psychoactive drugs. The 5 scales assessed (1) euphoria (Morphine-Benzedrine Group scale), (2) dysphoria (Lysergic Diethylamide scale), (3) sedation (Pentobarbital-Chlorpromazine-Alcohol Group scale), (4) intellectual efficacy and energy (Benzedrine scale), and (5) activation (Amphetamine scale).

Statistical Analysis

Statistical analyses were done employing the SPSS statistical program. For each parameter, mean and standard error (SE) were computed. The factor treatment was tested for significance (2-sided, $P \leq 0.05$) by using analysis of variance for repeated measures data. Bonferroni's correction was used to control for multiple comparisons with placebo ($P < 0.0125$ to reach significance), and these values were considered significant only if the overall treatment effect was significant at $P < 0.05$. Scales assessing alertness also included the factor Time (before versus after the driving test). Finally, ARCI-49 data was analyzed with a non-parametric Wilcoxon signed ranks test. Missing data was replaced by group means, but the analyses were also performed leaving out subjects with missing data, to determine whether this would change the statistical results. For driving tests that were terminated before completion, data collected during the last completed 10-km segment before stopping was used for each unfinished 10-km segment.

RESULTS

Participants

Bromfenac was recalled by its manufacturer during the data collection phase and the study was stopped before completion. Eighteen healthy volunteers (6 males and 12 females) completed the study. Their mean (SD) age was 24.0 (1.6) years, weight 66.2 (7.9) kg, and height 1.73 (0.06) cm. They used no concomitant medication other than oral contraceptives, and they had no history of alcohol or drug abuse. Visual acuity was normal for all participants. ECG recording, blood chemistry, hematology and urinalysis were within normal limits. None of the participants were positive on any breath alcohol test, urine drug screen or pregnancy test, and no abnormalities were found during physical examination. Participants possessed a driver's license and had driven more than 8000 km/yr during the preceding 3 years.

Failure to Complete Tests

In the oxycodone/paracetamol condition 2 females did not complete the evaluation due to side-effects, and the data on 1 female were lost. One terminated the driving test at 90 km, due to repeated vomiting and a second could not complete the laboratory test battery due to nausea, vomiting, and dizziness. Where possible, missing data were replaced with group mean data. A sensitivity analysis done after excluding these 3 women yielded almost the same results (not shown).

Results from the driving test, subjective assessments, and laboratory tests are summarized in Table 1.

The Driving Test

Although none of the treatments differed significantly in SDLP from placebo, a significant dose-response relationship was found for oxycodone/paracetamol ($P < 0.001$). The other driving test parameters did not show significant differences between any treatment and placebo.

Laboratory Tests

As is evident from Table 1, performance on the laboratory tests did not result in significant differences between the treatments and placebo.

Pupil Measurements

Mean pupil diameter for each treatment is shown in Figure 1.

Relative to placebo, the pupil diameter after oxycodone/paracetamol (5/325 mg and 10/650 mg) was significantly decreased ($P < 0.0001$). Significant differences from placebo are indicated in Figure 1 by an*. Also, there was a significant ($P < 0.001$) dose-response relationship for oxycodone/paracetamol. Relative to T1, pupil diameter was significantly decreased at T3 ($P < 0.007$) and T4 ($P < 0.006$).

Driving Related Subjective Assessments

Relative to placebo, mental effort during driving was significantly ($P < 0.0001$) elevated after oxycodone/paracetamol (10/650 mg), but not after the low dose of the drug. Also, a significant ($P < 0.001$) dose-response relationship was found for oxycodone/paracetamol. In contrast, mental effort after both doses of bromfenac did not differ significantly from the effort after placebo. Statistical analyses of perceived driving ability and mental activation did not reveal significant effects.

Alertness

Relative to that after placebo, alertness was significantly decreased after oxycodone/paracetamol 10/650 mg ($P < 0.0001$) and 5/325 mg ($P < 0.04$). Also, a significant ($P < 0.03$) dose-response relationship was found for oxycodone/paracetamol. In contrast, alertness did not differ significantly from that after placebo after both doses of bromfenac.

ARCI-49 Questionnaire

After the driving test, sedation was significantly increased in the oxycodone/paracetamol (10/650 mg) condition ($P < 0.01$). The high dose of oxycodone/paracetamol also significantly increased scores on dysphoria ($P < 0.003$). A significant ($P < 0.002$) dose-response relationship for oxycodone/paracetamol was found on dysphoria scores. After both doses of bromfenac and

TABLE 1. Results From the Driving Test, Subjective Assessments, and Laboratory Tests

	Placebo	Bromfenac 25 mg	Bromfenac 50 mg	Oxycodone/ Paracetamol 5/325 mg	Oxycodone/ Paracetamol 10/650 mg
Driving test					
SDLP (cm)	21.1 ± 1.0	20.5 ± 0.9	21.6 ± 0.9	20.5 ± 0.9	23.0 ± 1.3†
MLP (cm)	9.8 ± 3.5	10.1 ± 3.5	10.7 ± 3.1	8.0 ± 3.4	13.4 ± 3.7
SD speed (km/h)	2.9 ± 0.2	3.2 ± 0.2	3.2 ± 0.3	2.9 ± 0.2	3.4 ± 0.2
Mean speed (km/h)	88.7 ± 0.4	88.8 ± 0.4	89.7 ± 0.5	88.4 ± 0.3	88.2 ± 0.4
Subjective assessments					
Driving quality	10.3 ± 1.0	8.5 ± 0.7	8.6 ± 0.7	8.7 ± 0.7	6.4 ± 1.0
Mental effort	4.1 ± 0.6	4.5 ± 0.6	4.7 ± 0.7	5.0 ± 0.6	7.4 ± 0.8*†
Mental activation	12.8 ± 0.7	13.3 ± 0.6	13.1 ± 0.6	13.0 ± 0.9	12.9 ± 0.9
Tracking test					
Easy condition	8.4 ± 1.8	8.1 ± 1.8	7.3 ± 1.6	10.3 ± 2.2	11.3 ± 1.9
Hard condition	21.7 ± 1.6	21.2 ± 2.1	20.3 ± 2.0	22.5 ± 1.8	23.4 ± 1.7
Sternberg memory scanning test					
Reaction time (ms)	447 ± 18	447 ± 17	459 ± 18	466 ± 20	470 ± 17
% Errors	0.5 ± 0.08	0.5 ± 0.09	0.4 ± 0.07	0.4 ± 0.06	0.4 ± 0.08
Divided attention test					
Tracking	10.3 ± 2.0	10.8 ± 2.1	11.0 ± 2.1	12.0 ± 2.1	13.0 ± 2.1
Reaction time (ms)	517 ± 19	520 ± 21	520 ± 20	537 ± 28	550 ± 22
% Errors	4.8 ± 0.8	5.2 ± 0.9	3.9 ± 0.7	4.2 ± 0.7	3.9 ± 0.7

Mean ± SE are presented.
*Significant ($P < 0.0125$) differences from placebo.
†Significant ($P < 0.05$) dose-response relationships.
SDLP, standard deviation of lateral position; MLP, mean lateral position; SD, standard deviation.

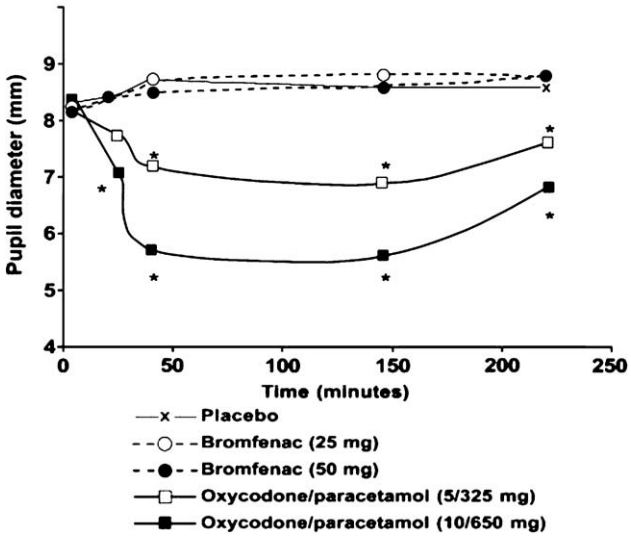

FIGURE 1. Mean pupil diameter (mm) measured at 5, 25, 40, 145 and 220 minutes after treatment administration. Significant differences ($P<0.05$) from placebo are indicated by *.

oxycodone/paracetamol (5/325 mg) no significant differences from after placebo were observed on any mood scale of the ARCI-49 questionnaire.

DISCUSSION

Relative to placebo, no significant treatment effects were found on driving ability. However, significantly increased mental effort during driving was reported after the high dose of oxycodone/paracetamol. Performance after oxycodone/paracetamol was worse than after placebo on all laboratory test parameters, but none of these differences reached statistical significance. Also, on most tests a dose effect was found for oxycodone/paracetamol. This dose-response effect was significant for SDLP (our primary parameter of vehicle control) and mental effort during driving.

Relative to placebo, the increment in SDLP after oxycodone/paracetamol 10/650 mg (+1.9 cm) is less than that observed with blood alcohol concentrations of 0.05 percent,[11] the legal limit for driving in most European countries. On the other hand, from Table 1 a clear dose-response effect is evident for oxycodone/paracetamol: performance was generally worse after the high dose of oxycodone/paracetamol. This was illustrated by the observation that some participants were unable to complete their laboratory test battery or driving test. Moreover, participants reported significantly increased sedation, reduced alertness, and increased mental effort while performing the driving test when treated with oxycodone/paracetamol. Thus, although group effects did not statistically differ from placebo effects, for some individuals the adverse effects produced by oxycodone/paracetamol were seriously disturbing, in such a manner that these subjects were unable to complete the scheduled test activities.

Experimental evidence on behavioral effects of ocycodone is scarce. One study[12] reported that oxycodone (0.13 mg/kg, intramuscularly injected) significantly impaired performance in tests measuring reaction time, body balance, critical flick fusion and attention, whereas tapping rate, eye-hand coordination, digit symbol substitution, and tracking were not significantly affected. The authors concluded that oxycodone primarily impaired cognitive functioning, not simple sensory motor functions.

A more recent study[13] showed that oxycodone (10 mg) produced no significant behavioral effects; however, a significant reduction in pupil size was found, and significantly increased sedation occurred. However, higher dosages of oxycodone (20 and 30 mg) did significantly impair performance on tests of eye-hand coordination, DSST, and logical reasoning. In our study, participants reported that considerably more effort was needed to perform the tests. It can be expected that at higher dosages performance impairment cannot be counteracted by participants motivation or increased efforts to conduct the tests. Thus, it is reasonable to assume that driving ability and other behavioral aspects will show significant impairment with dosages higher than 10 mg.

After both doses of bromfenac driving performance and the laboratory test results were comparable to those after placebo. Further, adverse effects after bromfenac were either mild or absent, and the drug did not significantly affect pupil size. No other behavioral studies have been performed with bromfenac and research with other NSAIDs is limited and yields inconclusive results.[14–19]

Sensitivity of the Tests and Participants to Drug-induced Impairment

The standardized driving test was developed in the 1980s and has been used in over 50 studies to determine the effects of various psychoactive drugs, including hypnotics,[20] antihistamines[21] and antidepressants on driving ability.[22] The primary parameter of the test, SDLP, has been shown to be sensitive to drug-induced impairment in a dose-dependent manner. The major advantage of this test is its realistic nature, an aspect that is difficult to simulate in the laboratory.[23] In previous studies, both our psychometric test battery and subjective assessments have proved to be sensitive to drug-induced and dose-dependent impairment.[24,25]

In our study, the sensitivity of the participants to the drug-induced effects was illustrated by the fact that both doses of oxycodone/paracetamol caused a significant reduction in pupil diameter. In humans, miosis (pupil size reduction) is a well-known physiological response observed after administration of opioid analgesics.[13,26–29]

Limitations of the Study

The limited number of participants that completed our study (N = 18), equals the number included in the study by Zacny and Gutierrez[13] and may explain the

absence of significant performance impairment after oxycodone/paracetamol. Presumably, if the intended number of participants had completed the study, more powerful and perhaps statistically significant results may have been found.

Our study was conducted in healthy volunteers. However, it has been shown that pain pathology itself may also have impairing effects on performance[30] that presumably will interfere with driving a car. Therefore, it is important to study the effects of analgesics on driving ability in pain patients. In addition, a substantial number of pain patients are elderly. Generalizing our results, which were obtained in young, healthy volunteers, may thus be problematic. The present study should therefore be conducted on the elderly as well.

In conclusion, additional research is needed to determine whether it is safe to drive a car while using opioid analgesics.

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