Federal Highway Research Institute (BASt)

Clinical Study Report

Effects of opioid analgesics on driving ability of pain patients

[Untersuchung zur Fahrsicherheit von Schmerzpatienten]

EUDRACT-No.: 2009-011774-15

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2 PRODUCT / SUBSTANCES

All patients were enrolled under their existent individual treatment as prescribed by their attending physician.

Opioid analgesics (only patients):	- Fentanyl (transdermal) - Buprenorphine (transdermal) - Oxycodone (sustained-release) - Hydromorphone (sustained-release) - Morphine (sustained-release)
Controls (only healthy volunteers)	- Alcohol (with orange juice; BAK = 0.5‰) - Placebo (orange juice)

3 STUDY TITLE

Effects of opioid analgesics on driving ability of pain patients [Untersuchung zur Fahrsicherheit von Schmerzpatienten]

EUDRACT-No.: 2009-011774-15

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4 STUDY CENTRES AND INVESTIGATORS

RESEARCH INSTITUTION (1)

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RESEARCH INSTITUTION (2)

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5 PUBLICATIONS

Ramaekers, J. G. (Hrsg.). (2011). *Effects of medicinal drugs on actual and simulated driving* (DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) Deliverable 1.2.2). Verfügbar unter www.druid-project.eu [21.06.2012].

Schumacher, M. (2014). Erfassung der Fahrsicherheit unter psychoaktiver Medikation am Beispiel der Langzeitanwendung von Opioiden bei chronischem Schmerz. Dissertation, Technische Universität Carolo-Wilhelmina Braunschweig. Verfügbar unter www.digibib.tu-bs.de/?docid=00056091 [18.06.2014].

Schumacher, M., Knoche, A., Jantos, R., Kaiser, M., Sabatowski, R. & Petzke, F. (2011). Einfluss von Opioiden auf verkehrsrelevante Leistungen. *Der Schmerz, 25, Supplement 1,* 148.

Schumacher, M., Knoche, A., Vollrath, M., Jantos, R., Vuurman, E., Petzke, F. et al. (2011). Effekte von Opioid-Analgetika im Fahrversuch. *Der Schmerz, 25, Supplement 1,* 147.

6 STUDIED PERIOD

01.11.2009 - 31.05.2011

7 PHASE OF DEVELOPEMENT

Phase IV – after market launch

8 TRIAL OBJECTIVES

To determine whether long-term treatment of chronic pain by opioid analgesics causes performance decrements in skills related to driving and in actual driving performance. Therefore a computer-based test of driving related skills was done as well as an on-the-road driving test. Performance of healthy controls, sober as well as under influence of 0.5g/L alcohol, was used as reference.

9 METHODOLOGY

According to the German Driving Licensing Act (FeV) five cognitive skills are relevant for safe driving (stress tolerance, visual orientation, ability, concentration, attention and reaction speed). These skills were assessed in this study by the Vienna Test System, a computer-based system developed for the assessment of fitness to drive. An overall sum score was defined as primary endpoint.

In addition, actual driving performance was assessed in a driving test on public roads. This test comprised two standardized procedures, the road-tracking test and the car-following test. For the road tracking test subjects drove 100km on a primary highway while lateral position of the car was continuously recorded. SDLP – a measure of weaving - was used as primary outcome measure. Duration of this test was one hour. The car-following test (Ramaekers, Muntjewerff, & O'Hanlon, 1995) involved the use of a second vehicle. Drivers had to follow this car. Thereby they had to adjust their driving speed to speed changes of this car to maintain a constant headway. In addition they had to react when the leading car was braking to reduce speed. Time to speed adaption (TSA) and brake reaction time (BRT) were calculated as performance measures.

This study compared performance of pain patients with the performance of an age-independent sample of healthy controls (23 to 58 years). Performance of healthy controls with blood alcohol

concentration (BAC) of 0.5g/L was used as reference. The amount of alcohol needed to raise BAC was calculated by the Watson formula. Breathalyzers were used to check BAC several times in the course of the driving test.

10 NUMBER OF PATIENTS

15 male and 11 female patients aged between 35 and 68 years (m= 54, sd = 8.28) suffering from non-cancer pain responsive to opioids were enrolled into this study. In addition 13 male and 8 female healthy controls participated in this study. Their mean (sd) age was 43 (10.68). Controls were selected from a pool of volunteers. 20 of 26 patients did the driving test in addition, so did 19 of 21 controls.

11 DIAGNOSIS AND CRITERIA FOR INCLUSION

General inclusion criteria (patients and controls)

- Written informed consent.
- Age: ≥ 30 ≤ 65: as far as possible three groups are built consisting of 10 persons each: 30-39, 40-49, 50-65
- Stable social background
- Body weight within 16-30 according to body mass index (BMI)
- Normal blood pressure and normal heart rate at rest
- Vision normal or corrected to normal
- Valid driver's license for passenger cars.
- Kilometres travelled per year: at least 2.000 km per year during preceding 12 month
- Driving on a regular basis: at least once per week
- Ability to drive a passenger car with manual transmission

Additional inclusion criteria only for pain patients

- Chronic non-cancer pain responsive to opioid analgesics
- Treatment for at least four weeks with
    - transdermal Fentanyl (e.g. Durogesic Smat®) ≥ 12 µg/h or
    - transdermal Buprenorphine (e.g. Transtec®) ≥ 10 µg/h or
    - oral, sustained-released Oxycodone (e.g. Oxygesic®) ≥ 10 mg/day or
    - oral, sustained-released Hydromorphone (e.g. Palladon®) ≥ 4 mg/day or
    - oral, sustained-released Morphine (e.g. Morphin HEXAL®) ≥ 20 mg/day
- No change in dose since 14 days

- Co-medication with NSAID and/or anticonvulsants and/or antidepressants on a constant dose at least since 14 days

Additional inclusion criteria only for controls

- Subjects who have restrained from eating 2 hours before the testing and who have restrained from drinking 1 hour before the testing.

General exclusion criteria (patients and controls)

- Subjects who fail to meet any of the inclusion criteria
- Persons who are imprisoned or are detained in a health mental institution by court or official order
- Malignant disease
- Severe disabilities that are expected to interfere with computerized testing or car driving
- Expected inability to drive the experimental car safely or to complete computerized testing or endangerment of being overstrained during the driving test or during computerized testing according to the estimation of the physician accomplishing the medical check up.
- Psychological or psychiatric disorders or severe physical disorders (history or current evidence of severe physical or mental disorders, serious gastrointestinal, hepatic, renal, cardiovascular or neurological disorders or severe allergies) that may interfere with participation in computerized testing or driving test
- Subjects with alcohol or drug abuse or dependency
- Unwillingness or inability to abstain from consumption of alcohol, psychoactive medication or drugs within 24 hours prior to the assessment day (urine drug screening, alcohol breath analyzer)
- Excessive smokers (more than 20 cigarettes a day) or excessive drinkers (more than 28 glasses of alcohol containing beverages per week)
- Regular intake of Benzodiazepines (≥ 4 times per week)
- Intake of Benzodiazepines within 2 days before assessment
- Regular intake of barbiturates (> 3 times per week) as well as intake of barbiturates within 2 prior to assessment
- Daily intake of high doses of antidepressants (Amitryptilin > 75mg, Doxepin > 75mg, Imipramin > 75mg, Trazodon > 100mg, Sertralin > 50mg, Fluoxetin > 20mg, Fluvoxamin >75mg, Duloxetin > 120mg, Venlafaxin > 225mg, Citalopram > 10mg)
- Daily intake of high doses of anticonvulsants (Carbamazepin > 1200mg, Oxcarbazepin >1800mg, Gabapentin >2400mg, Pregabalin >600mg)

- Intake of MAO inhibitors
- Regular intake of un-retarded opioids or intake of un-retarded opioids within 2 days prior to assessment
- Regular intake of antihistamines
- Inability to communicate meaningfully with the study staff (insufficient language skills)

Additional exclusion criteria only for controls

- Women who are pregnant or breast feeding or women of child-bearing potential who are not using a highly effective contraception method with a pearl-index <=1
- Subjects who are unable or unwilling to ingest alcoholic beverages
- Subjects with very infrequent alcohol consumption (less than one alcoholic beverage per month)
- Subject who are not able to consume the necessary amount of alcohol (self rating)
- former (voluntary disclosure) or actual alcohol dependency
- Subjects with known intolerance to alcohol
- Subjects who are taking concomitant medications which, in the opinion of the investigator, could impair driving ability or skills related to driving; or that could interfere with the absorption, distribution, metabolism, or excretion of alcohol
- Subjects taking medicaments prohibiting the consumption of alcohol

12 TEST PRODUCT

Opioid analgesics (chronic pain patients):	- Fentanyl (transdermal) - Buprenorphine (transdermal) - Oxycodone (sustained-release) - Hydromorphone (sustained-release) - Morphine (sustained-release)
Controls (healthy volunteers)	- Alcohol (with orange juice; BAK = 0.5‰) - Placebo (orange juice)

13 DURATION OF TREATMENT

No treatment. Pain patients were enrolled with their individual medication as prescribed by their attending physician.

14 REFERENCE THERAPY

no reference therapy

15 CRITERIA FOR EVALUATION

safety

16 STATISTICAL METHODS

SPSS 19 for Windows was used for all statistical analyses. Superiority testing by ANOVA for between group comparisons of patients and controls (sober) was used to test differences between both groups. Superiority testing by general linear model (GLM) repeated measures ANOVA with alcohol (two levels: 0.5‰ vs. sober) as main within subject factor was used to compare performance of controls being sober and being under influence of alcohol.

17 SUMMARY OF RESULTS AND CONCLUSIONS

Skills related to driving were assessed by a set of computer-based tests. An overall sum score summarizing the performance across all these tests was used as primary outcome measure. On this score pain patients under long-term treatment with opioid analgesics performed worse than healthy controls (Table 1). But in the alcohol calibration part of the study this set of computer-based tests has not proven to be sensitive to the impairment by alcohol. Hence the prerequisite for using this tests for the assessment of impairments by sedating drugs was not met in this study.

Table 1: Mean (SD) scores aus den Prozenträngen der Tests nach FeV und aller Tests (höhere Werte = bessere Leistung); P = Patienten, G = Gesunde.

group		ANOVA			
Patients (N = 26)	Controls (N = 21)	df	F	p ≤	η^2
46.82 (11.64)	57.76 (12.49)	1, 46	9.622	**.003**	.176

The primary outcome-measure (SDLP) of the road-tracking test had proven to be sensitive to alcohol effects. On this outcome measure patients did not perform worse than healthy controls (Table 2). Also the two measures of response time of the car-following test, TSA and BRT, were not impaired (Table 2).

Table 2: Mean (SD) of performance measures of the Road-tracking test and the Car-following test.

Performance measures	Patients (N = 20)	Controls (N = 19)	$p \leq$	η^2
SDLP (cm)	20.53 (4.29)	17.96 (4.04)	.062	.091
TSA (sec.)	3.17 (1.00)	3.26 (0.79)	.781	.002
RT (sec.)	0.93 (0.29)	0.86 (0.15)	.410	.018

The results of this study indicate that patients suffering from chronic non-cancer pain on stable doses of opioids are not necessarily unfit to drive. But due to the individual variability of test results an individual assessment is always recommended. Due to practical reasons no EEG measure was done. Also gaze direction was not assessed because the set-up time was too long and data quality was too low.

18 DATE OF REPORT

07.07. 2011