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Recovery and Simulated Driving after Intravenous Anesthesia with Thiopental, Methohexital, Propanidid, or Alphadione

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Recovery from anesthesia was assessed in a double-blind manner in 40 healthy volunteer students after intravenous anesthesia with thiopental (6.0 mg/kg), methohexital (2.0 mg/kg), propanidid (6.6 mg/kg), or alphadione (Althesin), 85 μl/kg using a driving simulator 2, 4, 6, and 8 hours after injection of the drugs. Clinical recovery was faster after propanidid and methohexital than after thiopental or alphadione. Driving performances remained significantly ($P < 0.05$) worse than in a control group for 6 hours after thiopental and for 8 hours after methohexital, and reaction times 8 hours after thiopental remained worse than in the control subjects. After alphadione driving skills were impaired at 6 hours only. Propanidid produced no impairment in driving skills at any time during the experiment. It is concluded that after the doses used in this study patients should not drive or operate machinery for at least 2 hours after propanidid and for at least 8 hours after alphadione. After methohexital and thiopental patients should probably not drive for 24 hours because of the severity of the disturbances at 8 hours. (Key words: Anesthetics, intravenous, thiopental; Anesthetics, intravenous, methohexital; Anesthetics, intravenous, propanidid; Driving; Anesthetics, intravenous, steroid; Anesthesia, outpatient.)

OUTPATIENT GENERAL ANESTHESIA is currently undergoing extensive evaluation as a means of increasing efficiency of patient care while at the same time decreasing its costs.[1–4] Success and safety of outpatient anesthesia depend on rapid recovery from the effects of the anesthetic as recovery is usually defined. Success and safety also, however, depend on duration of more subtle effects of anesthetics on psychomotor performance. There are many reports on time of gross recovery from anesthesia,[5–9] but only a few authors[10–12] have measured psychomotor performance such as driving ability after anesthesia. The present study was conducted to examine recovery and driving skills after three commonly used intravenous anesthetics, thiopental, methohexital, and the eugenol derivate, propanidid, and after a new steroid anesthetic, a combination of alphaxalone and alphadolone, alphadione (Althesin).

Material and Methods

SUBJECTS

Fifty volunteer students from the city of Helsinki were paid to participate in the study. All were in good health, and none had been on medication for at least a month prior to the experiment. Most subjects used alcohol, but only occasionally. Each subject held an valid driver's license and had maintained good driving ability by often driving a car. Informed consent was obtained from each subject for the procedure.

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TABLE 1. Characteristics of Test Groups and Injected Drug Doses

Treatment	Number of Volunteers	Age (Years) (Mean ± SD)	Weight (kg) (Mean ± SD)	Height (cm) (Mean ± SD)
None, control group	10	24 ± 2.2	76 ± 10	181 ± 5
Thiopental, 6.0 mg/kg	10	22 ± 2.1	65 ± 8	174 ± 7
Methohexital, 2.0 mg/kg	10	22 ± 2.8	67 ± 10	175 ± 9
Propanidid, 6.6 mg/kg	10	22 ± 2.5	65 ± 7	175 ± 6
Alphadione, 85 μl/kg	10	22 ± 2.2	68 ± 9	175 ± 7

DRUGS

The intravenous anesthetics used were 2.5 per cent thiopental sodium[¶] (6.0 mg/kg), 1 per cent methohexital sodium[**] (2.0 mg/kg), 5 per cent propanidid[††] (6.6 mg/kg), and the steroid combination alphadione[‡‡] (85 μl/kg). Each was injected into a forearm vein through a cannula in exactly 45 seconds. The intravenous position of the cannula was ascertained by checking the free flow of blood from the cannula and by injecting saline solution into the vein. Approximately 40 per cent oxygen was given for 5 minutes before and during the anesthesia by administering 8 l/min oxygen through a Ventimask (Vickers). Atropine sulfate[§§] was given intravenously 2 minutes before injection of the anesthetics.

TRIAL DESIGN

The subjects were assigned at random into five test groups of ten subjects each. Each group was comparable with respect to age, weight, and height (table 1). Four groups of ten subjects (two women in each) received an anesthetic and one group of ten subjects served as a control group. The latter was included to determine the possible effects of training on the test performances.

The same person introduced the driving simulator to all subjects in the same way. After the introduction subjects practiced for an hour with the simulator and were then tested once to provide pretreatment results.

The drugs were administered the next morning, and the subjects were tested in a double-blind manner 2, 4, 6, and 8 hours afterwards. Neither the volunteer nor the person testing him knew which anesthetic had been used. The subjects had abstained from eating and drinking for 8 hours before the anesthesia, and coffee, tea, cola, and tobacco were not allowed during the experiment.

ANESTHESIA AND IMMEDIATE RECOVERY

Both blood pressure and heart rate were followed during the experiment. Systolic and diastolic blood pressures were measured by auscultation.[13] Heart rate was recorded by counting the radial pulse. Measurements were taken after the subjects had been in a horizontal position for 5 min, after the injection of atropine, and 1, 2, 3, 5, 10, 15, and 20 minutes after injection of the anesthetics.

Different effects of the anesthetics were determined. Duration of sleep was assessed by recording the time until the subjects opened their eyes after repeated commands. Immediate recovery was assessed by recording the time until the subjects could sit and stand steadily with hands forward and eyes closed. Withdrawal reactions to the pinching of the lower abdomen were recorded, and amnesia was evaluated 1 hour after the injection on the basis of the subjects' ability to recall events during the recovery period (opening eyes, sitting, and standing). Apnea was assessed as cessation of regular thoracic movements. After each test period, *i.e.*, 2, 4, 6, and 8 hours after the injection of the anesthetics, the subjects were asked whether they felt tired or drowsy. They were also asked to assess their driving ability.

SIMULATED DRIVING

The simulator was a modified Sim-L-car,[14,15] which operated by a shadow projection of

[¶] Hypnostan, Leiras, Turku, Finland.

[**] Brevital sodium, Eli Lilly and Co., Indianapolis, Indiana.

[††] Propantan, Leiras, Turku, Finland.

[‡‡] Althesin, Glaxo, Greenford, England: a steroid combination of alphaxalone and alphadolone in a ratio 3:1.

[§§] Atropin, Orion, Helsinki, Finland.

a point source of light. The simulated moving roadway presented a densely populated as well as rural area with four intersections.[15,16]

The driving program used all possible roads, driving directions, and turns at crossroads. It was controlled by punched tape, and the same driving cycle appeared every 7 to 11 minutes, depending on the driving speed. Any time a driver approached an intersection, an arrow automatically appeared (left, right, straight on) to indicate the correct road. Each test period consisted of three driving cycles with a mean driving time of 30 minutes.

Emergency situations, in which a car drove from a yard in front of the experimental car, occurred three times during every experiment. Brake reaction times, as well as alterations in pulse rate in response to the emergency situation, were automatically measured. The emergency situations were programmed at certain points along the road. A television camera situated over the road disk was used to record the movements of the light source, *i.e.*, the experimental car on the road, and made it possible to record performance errors: collisions, neglected instructions and driving off the road (table 2).

TABLE 2. Variables Recorded during Simulated Driving

Electrical recordings
Steering wheel reversals
Number of times brake applied
Number of times clutch used
Number of times turning signal was used
Continuous recording of speed
Continuous recording of shifting
Brake reaction times
Driving times
Heart rate
Recording of error performance from a TV monitor
Collisions
Neglected instructions
Driving off the road

STATISTICS

Additivity of the results and within-cell variances were checked, and thereafter Student's t test and the two-way analysis of variance were used for the statistical treatment of the data.

Results

ANESTHESIA AND IMMEDIATE RECOVERY

All doses of the drugs administered produced a depth of anesthesia sufficient for minor surgical procedures, although withdrawal reactions seemed to occur more frequently after propanidid (70 per cent) than after the other drugs (30 to 50 per cent). Side effects during anesthesia were comparable in all groups (table 3). However, while

TABLE 3. Side Effects and Circulatory Changes after Intravenous Injection of Thiopental, Methohexital, Propanidid, or Alphadione

	Anesthetic*			
	Thiopental (6.0 mg/kg)	Methohexital (2.0 mg/kg)	Propanidid (6.6 mg/kg)	Alphadione (85 µl/kg)
Apnea	10 per cent	40 per cent	40 per cent	20 per cent
Involuntary muscle movements	0 per cent	40 per cent	40 per cent	40 per cent
Withdrawal reactions to abdominal pinching	40 per cent	50 per cent	70 per cent	30 per cent
Greatest decrease in systolic blood pressure (mm Hg)	15 ± 5	13 ± 4	20 ± 9	13 ± 9
Greatest decrease in diastolic blood pressure (mm Hg)	8 ± 5	6 ± 7	14 ± 11	11 ± 8
Greatest increase in heart rate (beats/min)	31 ± 23	26 ± 12	39 ± 19	18 ± 16†

* Percentage or mean ± SD, ten subjects.
† $P < 0.05$ in comparison with propanidid.

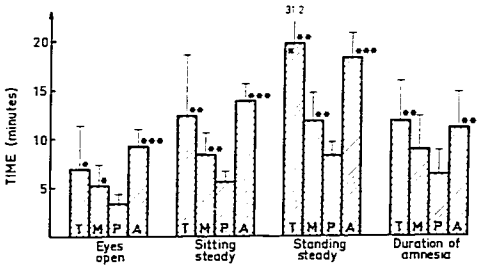

FIG. 1. Clinical recovery after intravenous anesthesia. Time for opening eyes, sitting steadily, standing steadily, and duration of amnesia after 6.0 mg/kg of thiopental (T), 2.0 mg/kg of methohexital (M), 6.6 mg/kg of propanidid (P), or 85 μl/kg of alphadione (A). Means ± SD, ten subjects. * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$ in comparison with propanidid; in comparison with methohexital × = $P < 0.05$

no involuntary muscle movements were noticed after thiopental, 40 per cent of the subjects who received other anesthetics had slight to moderate involuntary muscle movements. Changes in blood pressure and heart rate were greatest after propanidid. Apnea lasting approximately 30 seconds was associated with each anesthetic (10 to 40 per cent of subjects).

Recovery from the effects of the anesthetics varied. Duration of sleep was longest after the steroid combination, 9.3 ± 1.9 minutes, and shortest after propanidid, 3.5 ± 1.0 minutes (fig. 1). Sleep times after thiopental and methohexital were also significantly ($P < 0.05$) longer than after propanidid. The times elapsed until the subjects could sit or stand steadily and the time intervals between the opening of the eyes and standing steadily (average: propanidid 5.9, methohexital 6.6, steroid combination 9.1 and thiopental 12.5 minutes), were shortest after propanidid and longest after thiopental and alphadione. Subjects treated with propanidid could stand steadily with their eyes closed at a time when the subjects given alphadione had not yet opened their eyes (fig. 1). The durations of amnesia after thiopental (12 ± 4.1 min) and after alphadione (11 ± 3.7 min) were significantly ($P < 0.01$) longer than after propanidid (6 ± 2.5 min) and slightly longer than after methohexital (9 ± 3.4 min).

Subjective Assessments of Recovery

Two hours after injection of the anesthetic, 80 to 100 per cent of the subjects felt tired. After 8 hours, 50, 50, 40, and 20 per cent of the subjects still felt tired after thiopental, methohexital, propanidid, and the steroid anesthetic, respectively.

The volunteers' assessment of their driving ability was the most pessimistic after alphadione, 0 and 30 per cent reporting normal driving ability 2 and 4 hours later, respectively (fig. 2). Six and 8 hours after alphadione or methohexital, however, 80 to 90 per cent of the subjects considered their driving ability normal, while only half of the subjects given propanidid and 70 per cent of those given thiopental felt their driving ability was normal 8 hours after injection.

Anesthesia with propanidid was the least pleasant. Only 40 per cent of the subjects considered it pleasant. With methohexital, alphadione, and thiopental, 90, 70, and 60 per cent, respectively, considered the anesthesia to be pleasant.

Simulated Driving

Subjects who received thiopental or methohexital made significantly (two-way analysis of variance, $P < 0.001$) more performance errors during the whole experiment than did either subjects given propanidid or the unanesthetized control subjects. The number of performance errors was significantly ($P < 0.05$) greater 6 hours after thiopental and 8 hours after methohexital compared with the control group (fig. 3).

Subjects given the steroid combination, alphadione, did not make more performance errors than the control subjects in the 2- or 4-hour test periods, but at 6 hours the number of performance errors was significantly ($P < 0.05$) higher after alphadione than in the

control group. At 8 hours, however, the results again resembled those observed in the control group.

Results after propanidid were similar to those of the control group over the whole experiment. No significant change in number of performance errors could be observed after propanidid at any test period.

Brake reaction times during emergency situations were the longest 2 and 4 hours after thiopental. At both 6 and 8 hours there was no significant difference among reaction times in the thiopental, methohexital, and control groups, although the reaction times of subjects in the thiopental and methohexital groups were still longer than those of the control group after 8 hours (fig. 4). After thiopental the reaction times remained significantly (two-way analysis of variance: $p < 0.001$) longer during the entire experiment than after propanidid or the steroid combination. Reaction times after methohexital were similar to those of the control subjects over the whole experiment, but significantly ($P < 0.01$) longer than those recorded after alphadione. The brake reaction times of the subjects given alphadione were significantly ($P < 0.01$) shorter than those of the control group. The reaction times in the 2- and 4-hour tests were significantly (Student's t test: $P < 0.05$) shorter after the steroid combination than after thiopental.

Each group, including the control group, made significantly ($P < 0.001$) fewer steering wheel reversals than in pretreatment tests, but

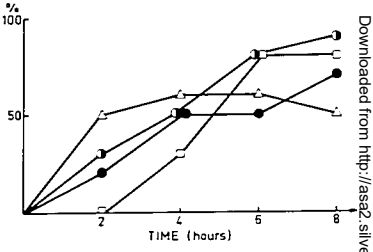

FIG. 2. Self-assessment of driving ability. Percentage of 10 subjects reporting their driving ability to be normal as a function of time after intravenous anesthesia with 6.0 mg/kg of thiopental (● —— ●), 2.0 mg/kg of methohexital (◑ —— ◑), 6.6 mg/kg of propanidid (△ —— △), or 85 μl/kg of alphadione (□ —— □).

at 8 hours the results resembled those of pretreatment tests. After alphadione there was a decrease in steering wheel reversals at 6 hours compared with those at 4 hours, and a similar tendency was observed with methohexital at 8 hours. Other variables measured during simulated driving did not change significantly compared with the control group.

Discussion

Subjects and Drugs

The criteria applied for choosing subjects were adequate to provide a homogeneous subject material for this type of study.[17]

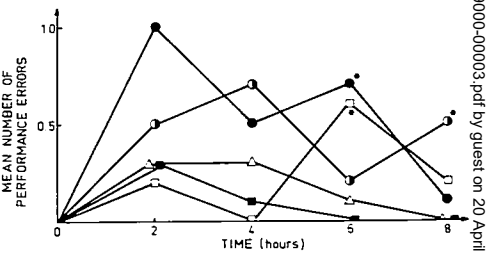

FIG. 3. The mean number of performance errors (neglected instructions, collisions, and driving off the road) during 30 minutes of simulated driving 2, 4, 6, and 8 hours after the intravenous administration of 6.0 mg/kg of thiopental (● —— ●), 2.0 mg/kg of methohexital (◑ —— ◑), 6.6 mg/kg of propanidid (△ —— △), and 85 μl/kg of alphadione (□ —— □). Ten subjects in each group. Student's t test: * = $P < 0.05$ in comparison with control group (■ —— ■); two-way analysis of variance: thiopental or methohexital vs. propanidid or controls, $P < 0.001$.

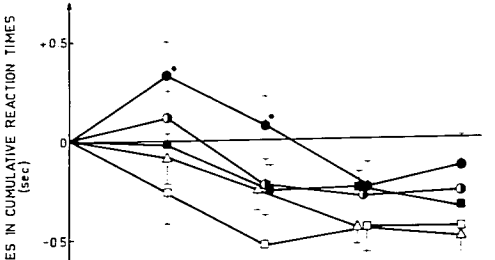

FIG. 4. Changes in the cumulative brake reaction times of three emergency situations during 30 minutes of simulated driving 2, 4, 6, and 8 hours after the intravenous administration of 6.0 mg/kg of thiopental (● —— ●), 2.0 mg/kg of methohexital (◑ —— ◑), 6.6 mg/kg of propanidid (△ —— △), and 85 μl/kg of alphadione (□ —— □), as well as those of the control group (■ —— ■). Means ± SE, ten subjects. Student's *t* test: * = $P < 0.05$ in comparison with alphadione; two-way analysis of variance: alphadione *vs.* controls, $P < 0.01$, thiopental *vs.* propanidid or alphadione, $P < 0.001$.

The doses of the drugs employed were based on those found in literature[18–27] and were those that should be adequate for minor dental and general surgery. Although large doses of atropine can cause dizziness, it is unlikely that the 0.5 mg dose of atropine used in the present study had any effect on the central nervous system that would impair psychomotor skills.[28]

According to the present results, the doses of anesthetics used were also roughly equipotent (table 3), although withdrawal reactions in response to pinching the abdomen seemed to be more pronounced and more frequent after methohexital and, especially, after propanidid, than after thiopental or alphadione. Furthermore, after 6.0 mg/kg thiopental and, especially, 85 μl/kg alphadione, sleep times were longer than following 2.0 mg/kg methohexital and, especially, 6.6 mg/kg propanidid (fig. 1). Therefore, from the point of view of outpatient surgery, minor surgical or painful diagnostic procedures lasting more than 5 minutes could probably be performed better with thiopental or alphadione than with propanidid or methohexital.

Trial Design and Driving Simulator

Since it was not desirable to repeat the anesthesia, the study was not done in a crossover fashion. However, a control group was included in the study to determine the possible effect of training on test performance. The control subjects did not receive atropine.

The test apparatus, Sim-L-car, has proven useful and suitable for investigating the effects of alcohol and drugs on driving skills.[14–16] Using the Sim-L-car, Green *et al.*[11] demonstrated impairment of skills after small doses of methohexital and thiopental, but in Wilkinson's study with a driving simulator[12] the impairment in acoustic or brake reaction times after methohexital anesthesia was brief and did not last longer than 20 minutes. The present modification of the apparatus had a complicated road system with four crossings and other vehicles on the road. One might expect that during the fairly monotonous driving, which lasted 30 minutes in the present experiment, the impaired alertness of the subjects would be more apt to lead to driving off the road, neglected instructions, or collisions in emergency situations than to alterations in single skills involved in driving. Häkkinen,[29] for example, has shown that accident-prone drivers have more difficulty handling the total driving situation than single skills.

Effects of Thiopental and Methohexital

The slow biotransformation of only 15 to 20 per cent of both thiopental[30] and methohexital[31] in an hour probably contributes to the delay in recovery observed after these agents. Earlier studies of thiopental and methohexital suggested that recovery would occur in 1 or 2 hours.[10,23,32,33] However, Doenicke *et al.* later demonstrated electroencephalographic sleep patterns 12 hours after 2 mg/kg methohexital[6] and impaired per-

formance in psychophysiologic tests 8 hours after 500 mg thiopental.[34] Although immediate clinical recovery (opening eyes, sitting and standing steadily) and psychomotor recovery 1 to 4 hours after anesthesia are faster after methohexital than after thiopental,[11,33,35,36] full psychomotor recovery, as also demonstrated in this study, takes the same time after both agents. Howells[37] came to the same conclusion when reviewing the literature. The present study confirms rapid initial recovery after methohexital, but driving skills remained severely impaired for at least 8 hours after 6.0 mg/kg thiopental or 2.0 mg/kg methohexital.

Effects of Propanidid

Propanidid is rapidly broken down enzymatically in man, none of the drug being detectable in serum within 1 to 2 hours after injection,[38,39] and none of its metabolites having any anesthetic potency.[30] These factors are probably the reason for the rapid recovery after propanidid. Doenicke *et al.*[6] and Schienle[40] found neither electroencephalographic sleep patterns 30 minutes or more after the injection of 500 to 1000 mg propanidid nor any deterioration of psychomotor performance 60 minutes after the drug had been administered. On the other hand, Rittmeyer[41] reported delayed reaction times in response to acoustic or optical stimuli 2 hours after propanidid anesthesia. In the present study clinical recovery occurred most rapidly after propanidid, and no significant impairment in simulated driving could be observed 2 hours or more after 6.6 mg/kg propanidid compared with controls. A greater dose of propanidid would have probably resulted in a longer sleep time, comparable to sleep times observed after the other anesthetics in this study, without causing any delay in clinical recovery, as demonstrated by Swerdlow and Moore.[42] The volunteers' pessimistic assessment of their driving ability after propanidid as compared with their driving performance might be considered a safety factor in traffic.

Effects of Alphadione

Alphadione consists of two steroids, one of which, alphaxalone, is pharmacologically the more active.[43] In animal studies the biological half-life of alphaxalone is 5 to 10 minutes,[44,45] and no residual signs of sleep have been observed in the electroencephalograms of rats.[46] However, Swerdlow[47] reported that after 80 μl/kg alphadione human subjects took 8.5 minutes before they could open their eyes and 14.2 minutes before they could sit steadily. Hannington-Kiff[48] reported that ocular imbalance, assessed by Maddox wing, returned to pretreatment levels only 90 minutes after injection of 50 μl/kg of alphadione. Our results, showing a longer sleep time and more prolonged clinical recovery with alphadione than after the other anesthetics tested, agree with those of Swerdlow.[47]

The simulated driving results in the alphadione group were better 2 and 4 hours after this combination than they were at comparable times following other anesthetics. However, impaired alertness recurred 6 hours after alphadione administration. This phenomenon has not been previously reported, and we have no explanation for it. Since all the variables measured during simulated driving indicated that alertness was impaired at 6 hours, it is unlikely that the observed recurrence of impaired performance after the steroid anesthetic was due to a methodologic error in the tests of mental alertness. One explanation might be that a metabolite of the steroids in alphadione has anesthetic potency and that an enterohepatic cycle results in impaired performance after eating. Furthermore, subjects given alphadione considered their driving ability to be poor 2 to 4 hours later, but after the 6-hour test 80 per cent of the subjects assessed their driving ability as normal (fig. 2). This sudden improvement in the subjective assessment of performance might have caused carelessness in handling emergency situations. The subjects' pessimistic self-assessment of driving ability 2 and 4 hours after alphadione might also have contributed to the better reaction times observed after alphadione than in controls. On the basis of the present material it is not possible to say whether a smaller dose of alphadione would have induced a shorter period of sleep and at the same time not caused recurrence of impaired performance 6 hours after the injection.

The results of this study concern young healthy subjects. The effects of these drugs on older or ill persons may be more harmful and may last longer.[37,42]

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Transfusion

TREATMENT OF INCOMPATIBLE BLOOD REACTION A 15-year-old white girl weighing 50 kg suffered multiple stab wounds to the chest and neck. During a two-hour period, she received 3,000 ml of A-positive blood. At this time, urine became deep red and arterial pressure began to decrease. At this time also the blood bank notified the authors that the patient's blood type was actually O-positive. Treatment with mannitol, O-positive packed cells, and crystalloid was instituted. Within 20 minutes, blood pressure was unobtainable and urinary output had ceased. Hemolysis, coagulopathy, and renal shutdown ensued. The authors undertook to provide massive hemodilution under moderate hypothermia and cardiopulmonary bypass. The patient was heparinized, a pump oxygenator system was primed with 4 liters of electrolyte solution containing sodium bicarbonate and calcium chloride, and cannulas were placed in the venae cavae and aorta. Bypass was instituted within three hours of admission. The patient's temperature was lowered to 27 C. Hemodilution progressed, resulting in hematocrit of 3 per cent within one hour after institution of bypass. The patient was then given a transfusion of O-positive erythrocytes while metabolic acidosis was corrected with appropriate infusions of bicarbonate. Clear urine began to appear and cardiopulmonary bypass was discontinued approximately three hours after its institution. Five and a half hours elapsed from the time massive transfusion reaction was diagnosed until the completion of operation. At the completion of operation, the patient was awake and responding. Following a period of controlled and intermittent mandatory ventilation, she made an uneventful recovery. She was discharged 14 days after admission without symptoms. The authors believe the patient represents the first survivor of a transfusion reaction following 3,000 ml of ABO-incompatible blood. (*Seager, OA, and others: Massive acute hemodilution for incompatible blood reaction. JAMA 229:790–792, 1974.*)