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Dexmedetomidine Decreases Thiopental Dose Requirement and Alters Distribution Pharmacokinetics

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Background: **α_2-Adrenergic agonists such as dexmedetomidine can be used to reduce the dose requirement of intravenous and volatile anesthetics. Whereas dexmedetomidine and volatile anesthetics interact pharmacodynamically (reduction of MAC), the mechanism of interaction between dexmedetomidine and intravenous anesthetics is not known.**

Methods: **Fourteen male ASA physical status 1 patients were randomly assigned to serve as control subjects (n = 7) or to be treated with dexmedetomidine (n = 7; 100, 30, and 6 $ng \cdot kg^{-1} \cdot min^{-1}$ for 10 min, 15 min, and thereafter, respectively). After 35 min, in all patients, thiopental (100 mg/min) was infused until burst suppression appeared in the raw tracing of the electroencephalogram. By using concentrations of thiopental in plasma and the electroencephalogram as a continuous pharmacologic effect measure, the apparent effect site concentrations for thiopental were estimated in both groups. Three-compartment pharmacokinetics were calculated for thiopental.**

Results: **Dexmedetomidine reduced the thiopental dose requirement for electroencephalographic burst suppression by 30%. There was no difference in estimated thiopental effect site concentrations between dexmedetomidine and control patients, suggesting the absence of a major pharmacodynamic interaction. Dexmedetomidine significantly decreased distribution volumes (V_2, V_3, and Vd_{SS}) and distribution clearances (Cl_{12} and Cl_{13}) of thiopental.**

Conclusions: **The thiopental dose-sparing effect of dexmedetomidine on the electroencephalogram is not the result of a pharmacodynamic interaction but rather can be explained by a dexmedetomidine-induced decrease in thiopental distribution volume and distribution clearances. Dexmedetomidine reduces thiopental distribution, most probably by decreasing cardiac output and regional blood flow. (Key words: Anesthetics, intravenous: thiopental. Interactions (drug): dexmedetomidine–thiopental. Sympathetic nervous system, α_2-adrenergic agonist: dexmedetomidine. Pharmacodynamics: thiopental. Pharmacokinetics: thiopental.)**

SOME α_2-adrenergic agonists[1] can be used as adjuvants in general and in regional anesthesia. A prototype, the centrally acting α_2-adrenergic agonist clonidine, has been shown to have sedative[2,3] and analgetic[4–6] properties. Clonidine, administered as a preanesthetic medication, reduces the subsequent dose requirement for intravenous anesthetics,[3,7] opioids,[8–10] and volatile anesthetics,[9–12] while revealing hemodynamically stabilizing characteristics during the induction of general anesthesia and surgery.[3,9,10,11,13,14]

Compared to clonidine, dexmedetomidine is a more specific and selective α_2-adrenergic receptor agonist with a shorter elimination half-life (1.6–2.4 *vs.* 7.4–13 h for clonidine).[15,16] Dexmedetomidine, administered as sole agent, is a sedative[16–19] and analgesic agent[20] with sympatholytic effects[15,17,21] similar those of to clonidine. Pretreatment with dexmedetomidine reduces, in patients, the dose requirement for the intravenous induction agent thiopental[22–26] and for opioids.[25–27] A reduction of the dose requirement also has been shown, in animal[28,29] and human studies,[26,30] for volatile anesthetics. Dexmedetomidine attenuates sympathoadrenal responses to painful stimulation during general anesthesia.[25,26,30]

Theoretically, a decrease in thiopental dose requirement after preanesthetic treatment with dexmedetomidine could be the result of a pharmacokinetic and/or a pharmacodynamic interaction of the two drugs.

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By using the electroencephalogram (EEG) as a pharmacologic measure of drug effect on the central nervous system (CNS) and by applying pharmacokinetic–pharmacodynamic modeling, it can be determined whether an altered dose requirement is based on a modified CNS sensitivity for a drug (a pharmacodynamic factor) or is based on modified drug disposition in the body (a pharmacokinetic factor).[31–34]

The current study had two goals: (1) quantitation of the impact of dexmedetomidine on thiopental dose requirement, using the EEG as a continuous pharmacologic effect measure and using EEG burst suppression as a pharmacologic endpoint for the thiopental dose requirement, and (2) determination of whether this dose-sparing effect is due to a pharmacokinetic, a pharmacodynamic, or a combined pharmacokinetic–pharmacodynamic mechanism.

Materials and Methods

The protocol of the current study was approved by the Committee for Medico-ethical Questions of the University of Berne. After written informed consent was obtained on the evening before elective surgery, the patients were randomly assigned to the dexmedetomidine group or control group in equal numbers. The study population consisted of 14 male ASA physical status 1 patients (age 20–46 yr and body weight 67–85 kg; table 1) scheduled for elective otolaryngologic or orthopedic surgery during general anesthesia. The health of the subjects was ascertained through medical history, a clinical examination, and routine laboratory tests. The subjects fasted overnight and arrived unpremedicated to the operating room. An antecubital vein was cannulated for the infusion of drugs. A radial artery catheter was used to monitor blood pressure and arterial blood gases and to collect blood samples for measurement of drug concentrations.

Electroencephalogram Recording

A bipolar EEG was recorded from frontooccipital leads F_{p1}–O_1 and F_{p2}–O_2 (international 10-20 system of electrode placement). At least 4 min of baseline EEG was recorded before administration of any drug, followed by continuous recording during the drug administration and subsequent recovery of consciousness. The EEG was recorded on an electroencephalograph (Encephaloscript E 16000, F. Schwarzer Ltd., Munich, Germany) with use of default settings (high-frequency filter 70 Hz, time constant 0.3 s, and sensitivity 10 μV/mm). The impedance of the electrodes was less than 3,000 ohm. The electroencephalograph was linked to a research system (Lifescan, Diatek Corporation, San Diego, CA) to store digitized EEG signals for off-line aperiodic waveform analysis.[35] The total number of waves per second was calculated from the EEG signal for use as a measure of CNS drug effect. The method of EEG recording and waveform analysis are described in detail elsewhere.[36,37]

Table 1. Demographic Data of Patients Studied

Patient (Initials)	Age (yr)	Weight (kg)	Height (cm)
Dexmedetomidine group			
BR	20	81	183
SK	24	70	175
GD	25	73	176
BW	28	72	180
HU	41	84	183
WH	43	67	171
NJ	46	75	173
Median	28	73	176
Control group			
HH	27	71	171
BU	27	75	173
AE	30	85	179
SA	36	83	185
GS	43	78	178
CR	44	75	168
LJ	45	75	173
Median	36	75	173

All 14 patients are male. The groups do not differ statistically in age, weight and height (Mann-Whitney test).

Drug Administration

In the control group, the recording of baseline EEG was followed by an infusion of physiologic saline for 35 min, after which thiopental (25 mg/ml) was given by an infusion pump (Precidor 5003, Infors AG, Basel, Switzerland) at a rate of 100 mg/min. The thiopental infusion was stopped when burst suppression appeared on the raw EEG tracing. Burst suppression was defined as an isoelectric period of at least 3 s between bursts of EEG waves. The patient was then allowed to recover and regain consciousness. When the patient was awake and verbally responsive, the EEG recording was terminated and general anesthesia for the scheduled surgery induced with methohexital. Arterial blood samples for the determination of thiopental concentrations in

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plasma (C_p) were obtained before thiopental administration and at 1-min intervals during the thiopental infusion and thereafter at gradually increasing intervals until the patient was transferred to the ward after the operation. Venous blood samples were collected 6, 8, 12, 18, and 24 h after the thiopental infusion. All thiopental blood samples were collected in sodium heparin tubes (Vacutainer, Becton Dickinson, Meylan Cedex, France).

In the dexmedetomidine group, the baseline (predrug) period was followed by an infusion of dexmedetomidine. To achieve and maintain a stable dexmedetomidine C_p of approximately 0.5 ng/ml at the time of thiopental infusion, computer simulations for an appropriate infusion regimen according to unpublished pharmacokinetic data‖ were performed. A dexmedetomidine C_p of 0.5 ng/ml has been reported to cause sedation without major side effects.[38,39] The infusion regimen for dexmedetomidine was designed as follows: 100 $ng \cdot kg^{-1} \cdot min^{-1}$ for the first 10 min after the baseline period, 30 $ng \cdot kg^{-1} \cdot min^{-1}$ for the following 15 min, and 6 $ng \cdot kg^{-1} \cdot min^{-1}$ thereafter. As in the control group, thiopental infusion was initiated at 35 min and terminated when burst suppression appeared in the EEG. Dexmedetomidine infusion and EEG recording were discontinued when the subject recovered consciousness. The succeeding general anesthesia and the blood sampling for the thiopental assay were performed as described for the control group. Arterial blood samples for the determination of dexmedetomidine C_p were drawn before the dexmedetomidine infusion; 10, 25, and 34 min after beginning of the dexmedetomidine infusion; at the end of the thiopental infusion (*i.e.*, at EEG burst suppression); and then once every hour until the end of surgery. All dexmedetomidine blood samples were collected in ethylenediaminetetraacetate tubes (Vacutainer, Becton Dickinson)

Responsiveness to verbal stimulation was examined intermittently. Oxygen by face mask was given while the subject was unconscious. Ventilation was assisted as necessary to keep arterial carbon dioxide tension within normal limits. Plasma was separated from blood cells and stored at −20°C for subsequent thiopental analysis. Plasma samples for dexmedetomidine analysis were shipped frozen to the Orion Corporation Farmos Research Center (Turku, Finland).

Chemical Assays

Total thiopental C_ps were measured by high-performance liquid chromatography.[40] The quantitation limit of the thiopental assay was 0.5 μg/ml. The coefficient of variation was less than 5% at 1.0 μg/ml. No interference occurred from dexmedetomidine or methohexital.

Dexmedetomidine C_ps were measured by gas chromatography–mass spectrometry[41] at Orion Corporation Farmos. The quantitation limit of the assay was 50 pg/ml, and the intraassay coefficient of variation ranged from 15% at 50 pg/ml to 6% at 500 pg/ml.

Data Analysis

Nonlinear least-squares regression analysis (MKMODEL)# was used to estimate thiopental pharmacokinetic parameters from the C_p *versus* time data. The data were fit to a three-compartment mamillary model with elimination from the central compartment.[42]

The thiopental EEG effect data were plotted against the concomitant C_ps. Because drug effect lagged behind the arterial C_ps, the resulting effect *versus* C_p profiles showed a hysteresis loop. The hysteresis reflects the disequilibrium between the drug concentration in the plasma and that at the site of effect. With the semiparametric modeling technique** described by Verotta and colleagues,[43,44] the disequilibrium can be estimated by using deconvolution to reduce or collapse the hysteresis loop. With this method, the apparent effect site concentration (C_e) (which is proportional to C_p at steady state) and the first-order equilibration rate constant (K_{e0}) between plasma and the effect compartment or the equilibration half-life ($T_{½}k_{e0}$), respectively, can be estimated for thiopental.[45,46] The application of this method is not limited by the biphasic (*i.e.*, not monotonic) nature of the concentration–effect relationship of thiopental. As shown previously, this method provides an estimate for $T_{½}k_{e0}$ and calculates C_e for each measured effect point, without prior knowledge of the pharmacokinetics or pharmacodynamics.[45,46]

The thiopental concentration *versus* EEG effect relationship is biphasic: thiopental first increases the EEG activity in the low concentration range (activation) and then depresses the EEG activity at higher concentrations

‖ Anttila M: Pharmacokinetics of dexmedetomidine in man after intravenous administration. Study Report October 15, 1988. Turku, Finland, Farmos Group Ltd. Research Center.

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(inhibition). The nonparametric method described by Bührer *et al.*[37] and Ebling *et al.*[46] was used to examine the relationship between C_e of thiopental and EEG effect. This allowed a model-independent evaluation of a potential influence of dexmedetomidine on the relationship between thiopental effect and apparent thiopental C_e. For each subject, the area under the EEG effect (waves per second) *versus* C_e curve (AUC) was calculated using a polynomial interpolating spline.[46] From the polynomial function, the following descriptors were calculated (fig. 1):

a. Initial number of waves per second (average number of waves per second immediately before thiopental administration in either group)
b. Total AUC of the EEG effect *versus* thiopental C_e relationship
c. Percentage of the AUC that represents EEG activation, above the initial number of waves per second
d. Thiopental C_e at the centroid (50% of the total AUC)
e. EEG effect at the centroid
f. C_e at the peak of EEG activation
g. Effect at peak EEG activation
h. C_e at return of initial number of waves per second
i. C_e at 50% of the initial number of waves per second.

The following nonparametric statistical tests were used: the Mann–Whitney test to examine differences between treatment groups (control *vs.* dexmedetomidine) and the Wilcoxon signed-rank test to examine differences within treatment groups. A P value of < 0.05 was considered statistically significant.

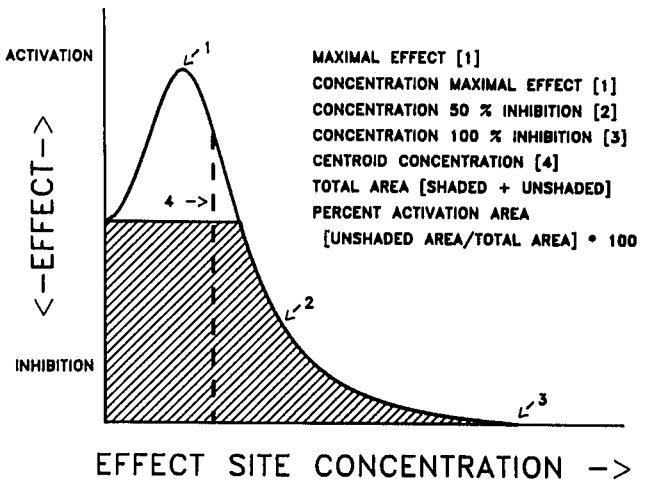

Fig. 1. Description of the biphasic relationship between drug concentration and electroencephalographic (EEG) effect, including the concentrations at certain defined EEG endpoints (points 1–4), maximal EEG *activation* (point 1), maximal EEG *inhibition* (point 3), and the total and activation areas described by the relationship. (Reproduced with permission.[46])

Results

All experiments in the 14 patients, as well the subsequent surgical procedures and postoperative period, were clinically uneventful.

All patients in the dexmedetomidine group were heavily sedated before the thiopental exposure: four subjects could be aroused on verbal command, but three subjects responded only to painful stimulation (trapezius squeeze). No sedation occurred in the control group.

The changes in hemodynamics were clinically acceptable and did not necessitate administration of any vasoactive drugs or additional intravenous fluids. Oxygen saturation was normal throughout the dexmedetomidine infusion. During the thiopental-induced unconsciousness, ventilation was assisted as needed by face mask. At the end of the thiopental infusion, median arterial oxygen tensions in the control and dexmedetomidine groups were 377 (range 290–424) and 412 (263–477) mmHg, respectively, and arterial carbon dioxide tensions were 50 (37–57) and 43 (32–57) mmHg, respectively.

Thiopental Dose Requirement

Thiopental was infused at 100 mg/min in all subjects until burst suppression (3 s isoelectricity) was noted in the EEG tracing. The dexmedetomidine treatment resulted in a significant decrease in the thiopental dose requirement compared to that of the control group (fig. 2): In the dexmedetomidine group, the median thiopental dose required was 574 mg (range 458–650 mg), whereas in the control group it was 833 mg (733–1325 mg; $P = 0.002$).

Pharmacokinetics

Although the thiopental administration rate during the first 5 min of drug infusion was identical in both groups, the median thiopental C_p at minute 5 was significantly higher in the dexmedetomidine group (50.9 μg/ml, range 42.0–62.4 μg/ml) than in the control group at the same time (36.6 μg/ml, range 31.4–43.6 μg/ml) (fig. 3). At the time of EEG burst suppression, there was no statistically significant difference in thio-

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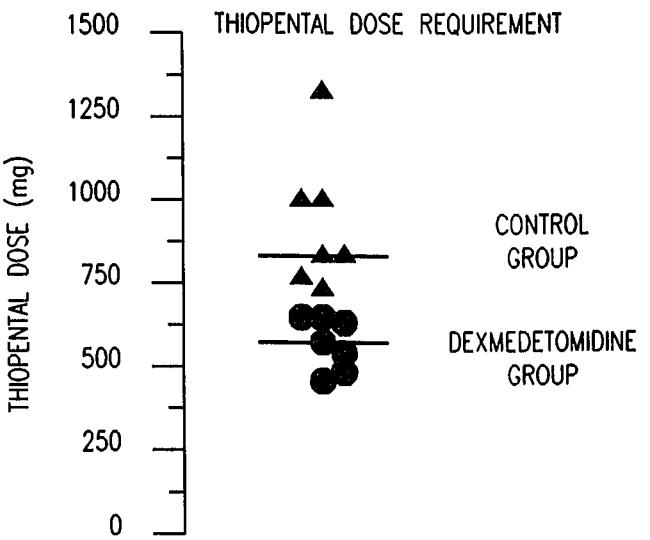

Fig. 2. Thiopental dose requirement for electroencephalographic (EEG) burst suppression is reduced by one third in dexmedetomidine patients (circles) compared to controls (triangles).

pental C_p between the two groups (dexmedetomidine group 59.6 μg/ml, range 46.2–83.3 μg/ml; control group 49.9 μg/ml, range 40.4–51.9 μg/ml).

The three-compartment pharmacokinetic analysis of the thiopental C_p (table 2) showed a statistically significant reduction in thiopental distribution volumes (V_2, V_3, and Vd_{ss}) and thiopental distribution clearances (intercompartmental) in the dexmedetomidine group. Body clearance, elimination half-life, and initial distribution volume of thiopental were not different between the two groups.

Pharmacodynamics

Before drug administration, the EEG effect parameter (waves per second) was stable (fig. 4A, control group). When thiopental was infused in the control subjects, the number of waves per second increased initially (activation) and then decreased until burst suppression (inhibition). After the thiopental infusion had been terminated, the patients demonstrated a progressive EEG activation pattern and recovered from unconsciousness. In the dexmedetomidine group (fig. 4B), the median number of waves per second decreased from 11.5 (range 10.0–14.0) to 9.2 (6.7–14.0) ($P < 0.05$) during the dexmedetomidine infusion before the thiopental administration. The visual inspection of the raw EEG tracing before thiopental administration revealed a loss of high-frequency waves and increase in high-amplitude slow waves, suggesting that dexmedetomidine caused the slight but statistically significant decrease in number of waves per second. The subsequent biphasic thiopental EEG effect, however, was similar in the two groups. The median dexmedetomidine C_p was 0.8 ng/ml (range 0.7–1.0 ng/ml) at the beginning and 0.9 ng/ml (0.8–1.0 ng/ml) at the end of the thiopental infusion (fig. 4C). Although the measured dexmedetomidine C_ps were greater than the target C_p (0.5 ng/ml), the C_ps in all patients were in the same range during the thiopental exposure.

Semiparametric pharmacodynamic analysis for thiopental was performed on the C_p and EEG data (waves per second) to estimate $T_{½}k_{eo}$ and C_e. $T_{½}k_{eo}$ values were in the range of 1–2 min (table 3) and in agreement with previously published data.[31,34,45] There was no statistically significant difference for thiopental $T_{½}k_{eo}$ between the two groups (table 3).

Although in the dexmedetomidine group a smaller amount of thiopental was required to produce EEG burst suppression, the apparent C_e of thiopental reached similar

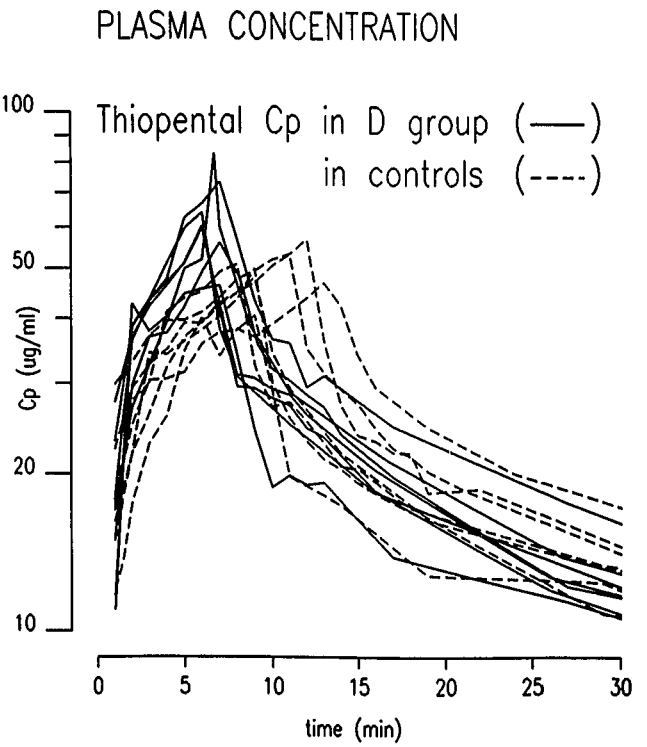

Fig. 3. Measured thiopental concentration in plasma (C_p) *versus* time profiles in the dexmedetomidine group (solid lines) and the control group (dashed lines). Thiopental was administered at an infusion rate of 100 mg/min in all patients until electroencephalographic burst suppression was observed. Note the more rapidly increasing C_ps in the dexmedetomidine group.

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Table 2. Thiopental Pharmacokinetics in Dexmedetomidine and Control Patients

Patient (Initials)	Cl (l/min)	K_{12} (min^{-1})	K_{21} (min^{-1})	K_{13} (min^{-1})	K_{31} (min^{-1})	V_1 (l)	V_2 (l)	V_3 (l)	Vd_{ss} (l)	Cl_{12}† (l/min)	Cl_{13}† (l/min)	Elimination $T_{1/2}$ (hr)
Dexmedetomidine group												
BR	0.144	0.151	0.096	0.081	0.0072	5.19	8.19	58.3	71.7	0.783	0.419	7.2
SK	0.175	0.196	0.111	0.072	0.0066	4.35	7.68	47.5	59.5	0.852	0.313	5.5
GD	0.155	0.588	0.184	0.138	0.0085	2.69	8.59	43.5	54.8	1.581	0.371	5.3
BW	0.178	0.232	0.060	0.043	0.0036	4.39	17.1	53.2	74.7	1.018	0.189	7.6
HU	0.209	0.532	0.106	0.129	0.0039	3.21	16.1	106.7	126.0	1.707	0.414	9.9
WH	0.158	0.247	0.212	0.123	0.0109	4.90	5.71	55.3	65.9	1.210	0.602	5.8
NJ	0.203	0.759	0.201	0.150	0.0068	2.36	8.91	51.8	63.1	1.791	0.354	5.1
Median	0.175	0.247	0.111	0.123	0.0068	4.35	8.59	53.2	65.9	1.210	0.371	5.8
Control group												
HH	0.267	0.344	0.134	0.120	0.0083	5.28	13.5	76.2	95.1	1.816	0.633	5.3
BU	0.142	0.426	0.111	0.106	0.0080	4.19	16.1	55.7	76.0	1.784	0.444	7.4
AE	0.249	0.669	0.108	0.163	0.0056	3.61	22.3	105.8	131.8	2.415	0.588	8.0
SA	0.194	0.296	0.085	0.086	0.0046	6.89	23.7	127.9	158.5	2.039	0.589	11.9
GS	0.154	0.492	0.110	0.133	0.0078	4.25	19.0	72.7	96.0	2.091	0.565	8.6
CR	0.231	0.810	0.137	0.211	0.0065	2.75	16.2	89.5	108.5	2.227	0.580	7.1
LJ	0.193	0.931	0.112	0.368	0.0056	1.93	16.0	126.6	144.5	1.796	0.710	10.8
Median	0.194	0.492	0.111	0.163	0.0065	4.19	16.2	89.5	108.5	2.039	0.588	8.0
	NS	NS	NS	NS	NS	NS	*	*	*	*	*	NS

NS = not significant.

* $P < 0.05$ (Mann–Whitney test).

† $Cl_{12} = V_1 \cdot K_{12}$; $Cl_{13} = V_1 \cdot K_{13}$.

peak values in both the dexmedetomidine and control groups (dexmedetomidine group median 47.7 μg/ml, range 37.4–55.3 μg/ml; control group median 43.1 μg/ml, range 36.9–52.9 μg/ml; $P > 0.1$) (fig. 5).

The similarity of the thiopental CNS effect in both the control and dexmedetomidine groups also can be summarized by the nonparametric pharmacodynamic descriptors derived from the EEG effect *versus* C_e profiles (table 3): AUC and C_e at the peak of activation, at the time of return to 50% of initial effect values, and at the return to initial effect values did not differ substantially. Furthermore, the moderately lower values of EEG effect measured before thiopental administration and at the peak of activation in the dexmedetomidine group did not differ statistically from those in the control group. The only statistically significant difference in these descriptors was in the EEG effect values predicted for the centroid (which divides the total AUC into two areas of equal size; fig. 1). The lower median EEG effect value at the centroid in the dexmedetomidine patients compared to the corresponding value in the control group (11.8 *vs.* 14.9 waves/s; table 3) may be due to the general slight decrease of the EEG *versus* C_e profiles in the dexmedetomidine group (see above).

The effects of dexmedetomidine and thiopental on hemodynamic parameters are summarized in figure 6 and table 4. Mean arterial blood pressure in the thiopental group at the time of maximal inhibitory EEG effect (burst suppression) did not differ significantly from mean arterial blood pressure before thiopental administration. In the dexmedetomidine group, however, mean arterial blood pressure decreased significantly, by approximately 25%, during the 35 min of dexmedetomidine infusion (fig. 6). This hypotension became even more evident at the time of burst suppression and the subsequent 20 min. In the control subjects, administration of thiopental was accompanied by an increase in heart rate; the dexmedetomidine subjects demonstrated a significant slowing in heart rate during the time before thiopental infusion and showed only a moderate increase in heart rate at the time of burst suppression (table 4).

Discussion

Clonidine, the prototype of the α_2-adrenergic agonists, has been used as an anesthetic adjuvant[8] since 1986. Dexmedetomidine, a novel α_2-adrenergic ag-

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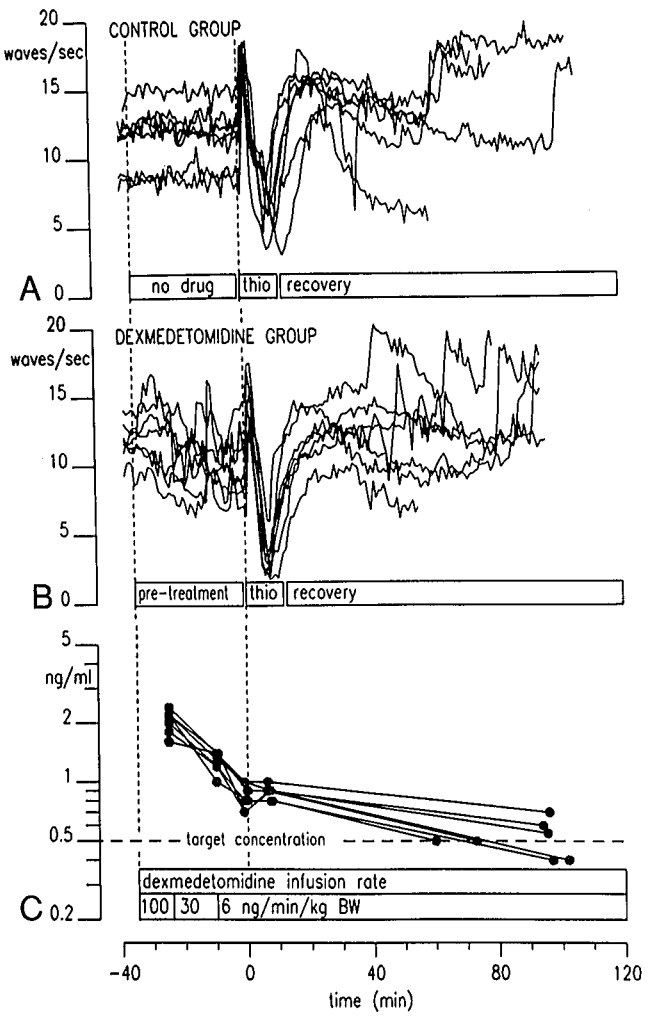

Fig. 4. The electroencephalographic (EEG) drug effect parameter (waves per second) and the measured dexmedetomidine concentrations in plasma. (*A*) EEG drug effect parameter *versus* time profiles in the control group. The EEG parameter was stable at baseline (*left*, vertical dashed line) and during the 35 min of recording before the thiopental infusion (*right*, vertical dashed line). The biphasic thiopental effect (activation at the beginning and inhibition at the end of the thiopental infusion) is reflected by an increase and decrease in the number of waves per second. (Because of parameter processing, for graphic purposes the observed burst suppression cannot be displayed in the figure as "zero waves per second.") After cessation of the thiopental infusion, the effect measure revealed fluctuating activation patterns at the time of awakening. (*B*) EEG effect parameter *versus* time profiles in the dexmedetomidine group. The EEG parameter shows gradual deceleration during the dexmedetomidine infusion. The median number of waves immediately before the start of thiopental infusion (initial EEG) is less than that before the start of dexmedetomidine infusion (baseline EEG; 9.2 *vs.* 11.5 waves/s, $P < 0.05$). EEG effect values at baseline, before thiopental infusion, at activation, and at inhibition do not differ statistically from those of the control group. (*C*) Measured dexmedetomidine concentrations in plasma in the dexmedetomidine group. Dexmedetomidine was infused as follows: 100 ng·kg^{-1}·min^{-1} for 10 min, 30 ng·kg^{-1}·min^{-1} for 15 min, and 6 ng·kg^{-1}·min^{-1} thereafter. This infusion scheme provided fairly constant dexmedetomidine concentrations in plasma between the beginning and the end of the thiopental infusion.

onist, is also known to have sedative and anxiolytic effects and is therefore considered to have potential as an preanesthetic medication.[24,47,48] Relative to clonidine, dexmedetomidine is a more specific α_2-agonist and has a shorter terminal elimination half-life.[15,16]

Using clinical endpoints such as loss of eyelash reflex, it has been shown that dexmedetomidine administered as premedication resulted in a remarkable reduction of thiopental dose requirement.[22-26] In the current study, EEG burst suppression was used as an endpoint for the thiopental dose requirement. This EEG endpoint has been used previously to examine the impact of age[31,33] or chronic alcohol intake[34] on thiopental requirement. Dexmedetomidine pretreatment (approximately 100 μg/70 kg infused over 35 min) reduced the thiopental dose requirement by 30%. This thiopental dose-sparing effect is on the same order of magnitude as that of similar dexmedetomidine doses in studies that have used clinical endpoints for thiopental administration.[22,24-26]

Theoretically, the reduction in thiopental dose requirement in the dexmedetomidine group could be the expression of a direct dexmedetomidine effect on the CNS (pharmacodynamic effect), of a dexmedetomidine effect on the pharmacokinetics of thiopental, or of a combination of a pharmacokinetic and pharmacodynamic drug interaction. These possibilities are considered below.

Pharmacodynamic Interaction

Although the α_2-adrenergic agonists caused some slowing in the EEG (a decrease of high-frequency waves and increase of high-amplitude slow waves),[8,49,50] our study did not provide evidence for a substantial pharmacodynamic interaction (additive or synergistic) of dexmedetomidine with thiopental. At the time of EEG burst suppression, the calculated C_e of thiopental was the same in both the control and dexmedetomidine groups. This suggests that brain sensitivity for thiopen-

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Table 3. Thiopental Pharmacodynamics in Dexmedetomidine and Control Patients

Patient (Initials)	Initial EEG (waves/s)	AUC Total (waves · μg/s · ml)	AUC Activated (%)	Ce at Centroid (μg/ml)	EEG at Centroid (waves/s)	Ce at Maximal EEG Activation (μg/ml)	EEG at Maximal Activation (waves/s)	Ce at Return of Initial EEG (μg/ml)	Ce at 50% Return of Initial EEG (μg/ml)	$T_{1/2}k_{e0}$ (min)
Dexmedetomidine group										
BR	6.7	367.4	21.0	17.9	10.0	13.2	11.8	27.3	34.5	1.3
SK	11.0	590.4	11.9	19.9	12.0	6.4	17.6	23.8	45.2	2.0
GD	8.9	461.4	25.2	19.8	11.8	16.7	13.0	30.3	40.3	1.4
BW	9.2	491.9	15.2	19.2	10.7	8.5	16.2	24.8	40.0	1.4
HU	14.0	598.4	7.6	18.0	13.8	5.9	19.2	17.3	36.5	2.2
WH	8.4	444.1	18.2	18.6	11.0	7.8	13.5	28.3	37.3	1.7
NJ	11.2	514.2	9.7	20.2	14.1	16.7	14.9	29.3	35.4	1.9
Median	9.2	491.9	15.2	19.2	11.8	8.5	14.9	27.3	37.3	1.7
Control group										
HH	11.9	587.7	12.8	19.3	15.9	11.8	16.8	25.6	41.2	1.4
BU	12.2	669.4	12.7	21.8	16.0	18.8	17.3	29.6	45.6	1.3
AE	7.4	387.4	25.4	16.3	16.1	15.1	16.7	25.8	35.0	1.3
SA	9.2	511.1	26.0	16.4	12.8	11.6	18.0	29.7	36.8	2.0
GS	13.2	639.6	8.9	20.0	14.9	6.9	18.8	21.9	40.0	1.2
CR	14.7	608.4	5.8	19.0	12.6	7.3	18.5	14.8	40.8	1.8
LJ	12.4	715.7	11.0	23.2	14.7	13.5	17.6	26.4	50.1	1.0
Median	12.2	608.4	12.7	19.3	14.9	11.8	17.6	25.8	40.8	1.2
	NS	NS	NS	NS	*	NS	NS	NS	NS	NS

EEG = electroencephalogram; initial EEG = waves/s before thiopental administration; AUC = area under the curve (EEG effect *vs.* Ce); Ce = apparent effect site concentration; $T_{½}k_{e0}$ = half-life of equilibration between plasma and effect compartment; NS = not significant.

* $P < 0.05$ (Mann-Whitney test).

tal was not altered, as it would be in the case of an additive or synergistic effect. The clearly sedative effect of dexmedetomidine observed before the thiopental administration did not lead to a decrease of thiopental C_e estimated from EEG data.

The lack of apparent pharmacodynamic synergism of dexmedetomidine and thiopental when the EEG is used as a pharmacologic measure of CNS drug effect contrasts with the synergistic effect of dexmedetomidine with volatile agents, in which dexmedetomidine decreases MAC, the standard clinical measure of anesthetic depth.[26,28–30] A reduction in MAC is evidence for a pharmacodynamic interaction and is not explained by any pharmacokinetic alteration of volatile anesthetics by dexmedetomidine. These observations may reflect two issues: (1) EEG burst suppression is not correlated with clinical measures, such as movement, in the MAC concept, and (2) dexmedetomidine has different mechanisms of interaction for different classes of anesthetics (barbiturates *vs.* volatile anesthetics).

Pharmacokinetic Interaction

Thiopental was infused in all subjects at 100 mg/min. Although smaller doses of thiopental were administered in the dexmedetomidine group, the thiopental C_p at the time of burst suppression was the same in both groups. This can be explained by decreased distribution volumes (V_2 and V_3) and intercompartmental clearances of thiopental in the dexmedetomidine group (table 2); *i.e.*, thiopental movement from the central compartment was significantly reduced by dexmedetomidine administration.

Reduced thiopental dose requirement and distribution to body tissues can be explained, at least in part, by the dexmedetomidine effect on the hemodynamic system: arterial blood pressure in the dexmedetomidine group was substantially decreased by the α_2-agonist treatment before the thiopental infusion and, in contrast to the blood pressure in control patients, even more at the time of the thiopental-induced EEG burst suppression. Whereas in the control patients, prominent tachycardia developed

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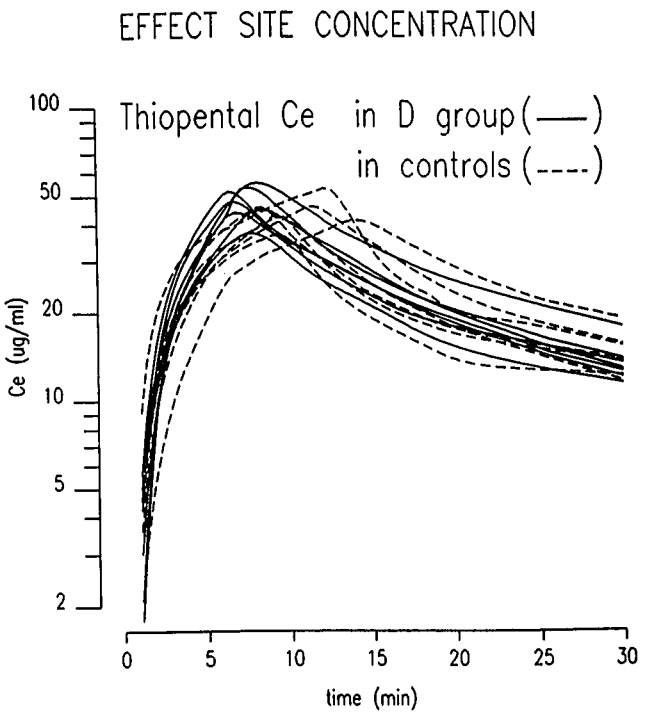

Fig. 5. Apparent effect site thiopental concentration (C_e) *versus* time profiles in the dexmedetomidine group (solid lines) and the control group (dashed lines). Thiopental was administered at an infusion rate of 100 mg/min in all patients until electroencephalographic burst suppression was observed. Note that peak concentrations at the effect site are not different.

at burst suppression, the heart rate increased in dexmedetomidine patients to a smaller extent. From a hemodynamic point of view, the dose-sparing effects created by either α_2-agonist or β-antagonist (*i.e.*, β-blocking agent) administration are intriguingly similar: Stanley *et al.*[51] showed that patients premedicated with propranolol had both a lower heart rate and lower blood pressure at the beginning of a sufentanil infusion (300 μg/min) and required 25% less sufentanil to create unconsciousness relative to control patients.

Other studies have shown that dexmedetomidine reduces circulating norepinephrine.[17,23,48] There is evidence that the centrally and peripherally mediated sympatholytic action of dexmedetomidine is the direct cause for the decrease in blood pressure and cardiac output and that bradycardia is generated by an increase of the parasympathetic tone.[15,21,52] Bloor *et al.*[21] observed in humans an average decrease from baseline blood pressure by 25%, heart rate by 10%, and cardiac output by 15% in the presence of an average dexmedetomidine C_p of 0.6 ng/ml, which is similar to the dexmedetomidine C_p in our study (0.7–1.0 ng/ml).

In the current study, cardiac output was not measured. Nevertheless, the profiles of both blood pressure and heart rate in the dexmedetomidine group (fig. 6) could be an indicator of reduced cardiac output and decreased regional blood flow and hence be the major factor for the altered distribution kinetics of thiopental. The influence of presumably altered cardiac output on thiopental pharmacokinetics represents a similar mechanism, as it can be postulated for the altered distribution kinetics and reduced dose requirement when tissue perfusion is decreased (*e.g.*, in hemorrhagic shock, congestive heart failure, or advanced age).[53–57]

The current study demonstrates a significant reduction of the thiopental distribution by the α_2-adrenergic agonist. Most likely the same pharmacokinetic mechanism has been observed with alfentanil in presence

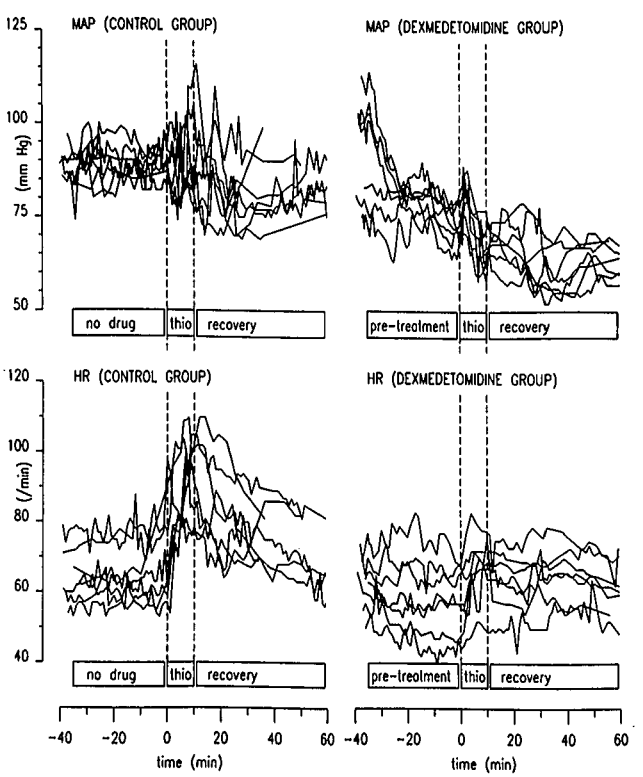

Fig. 6. Hemodynamic parameters: time course of mean arterial pressure (MAP; *top*) and heart rate (HR; *bottom*) in the control group (*left*) and dexmedetomidine group (*right*). In the dexmedetomidine group, MAP decreased significantly during the 35 min of dexmedetomidine infusion (pretreatment) and decreased gradually throughout the observation period. The obvious increase in HR in the control group during the thiopental exposure was not observed in the dexmedetomidine group.

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Table 4. Cardiovascular Parameters: MAP and HR at Baseline, before Infusion of Thiopental, and at Burst Suppression

	Control Group	Dexmedetomidine Group
MAP (mmHg)		
At baseline (predrug)	87 (84–95)	99 (76–111)
Before thiopental	88 (83–94)	73 (66–78)*†
At burst suppression	86 (77–105)	68 (61–77)*†
HR (beats/min^{-1})		
At baseline (predrug)	63 (54–78)	63 (51–72)
Before thiopental	63 (56–79)	57 (45–69)*
At burst suppression	85 (73–105)*	67 (50–76)*†

All values are median and (range).

MAP = mean arterial blood pressure; HR = heart rate.

* Different from previous value within the group (Wilcoxon signed-rank test).

† Different from corresponding value in the other group (Mann–Whitney test).

of an α_2-agonist: Segal *et al.*[58] administered alfentanil at an identical infusion rate in clonidine-treated and control patients and found significantly higher C_ps for alfentanil in clonidine-treated patients. Alfentanil distribution kinetics are known to be largely determined by cardiac output.[56]

The use of dexmedetomidine may have important implications for the rationale for dosing intravenous anesthetics or opioids that rely on distribution mechanisms to terminate effects. To avoid potential anesthetic overdosing in patients treated with dexmedetomidine, it is necessary to examine the pharmacokinetics of commonly used intravenous anesthetics and opioids with and without concomitant dexmedetomidine. Patients having impaired hemodynamic status and reduced sympathetic tone by an α_2-adrenergic agonist such as dexmedetomidine may particularly be threatened by the "normal" dose of intravenous anesthetics or opioids.

The clinical indications for dexmedetomidine and α_2-agonists in general for anesthetic practice are not yet clearly defined, but research is being undertaken to define them.[1] Our study suggests that pharmacokinetic mechanisms could explain the interaction of thiopental and dexmedetomidine. As indications for the use of dexmedetomidine increase, it will be compulsory to differentiate between the pharmacokinetic and a potentially pharmacodynamic nature of the interaction of dexmedetomidine with anesthetics to use these compounds rationally.

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