Enzyme-inducing Anticonvulsants Increase Plasma Clearance of Dexmedetomidine

A Pharmacokinetic and Pharmacodynamic Study

Alana M. Flexman, M.D., Harvey Wong, Ph.D., K. Wayne Riggs, Ph.D., Tina Shih, M.D., Paul A. Garcia, M.D., Susana Vacas, M.D., Pekka O. Talke, M.D.

ABSTRACT

Background: Dexmedetomidine is useful during mapping of epileptic foci as it facilitates electrocorticography unlike most other anesthetic agents. Patients with seizure disorders taking enzyme-inducing anticonvulsants appear to be resistant to its sedative effects. The objective of the study was to compare the pharmacokinetic and pharmacodynamic profile of dexmedetomidine in healthy volunteers with volunteers with seizure disorders receiving enzyme-inducing anticonvulsant medications.

Methods: Dexmedetomidine was administered using a step-wise, computer-controlled infusion to healthy volunteers (n = 8) and volunteers with seizure disorders (n = 8) taking phenytoin or carbamazapine. Sedation and dexmedetomidine plasma levels were assessed at baseline, during the infusion steps, and after discontinuation of the infusion. Sedation was assessed by using the Observer's Assessment of Alertness/Sedation Scale, Ramsay Sedation Scale, and Visual Analog Scale and processed electroencephalography (entropy) monitoring. Pharmacokinetic analysis was performed on both groups, and differences between groups were determined using the standard two-stage approach.

Results: A two-compartment model was fit to dexmedetomidine concentration–time data. Dexmedetomidine plasma clearance was 43% higher in the seizure group compared with the control group (42.7 *vs.* 29.9 l/h; $P = 0.007$). In contrast, distributional clearance and the volume of distribution of the central and peripheral compartments were similar between the groups. No difference in sedation was detected between the two groups during a controlled range of target plasma concentrations.

Conclusion: This study demonstrates that subjects with seizure disorders taking enzyme-inducing anticonvulsant medications have an increased plasma clearance of dexmedetomidine as compared with healthy control subjects. **(ANESTHESIOLOGY 2014; 120:1118–25)**

DEXMEDETOMIDINE is often used during anesthesia for neurosurgical procedures due to several unique properties. Dexmedetomidine is a selective α-2 agonist and induces sedation by reducing norepinephrine release from locus coeruleus.[1] This relatively short-acting sedative agent is ideally suited for procedural sedation during neurosurgical procedures as patients become sedated yet arousable and cooperative when required. Undesirable brain swelling due to hypercapnea is avoided as dexmedetomidine causes minimal respiratory depression compared with other anesthetic agents.[2] Finally, dexmedetomidine has been shown to be useful during mapping of epileptic foci with general anesthesia as it does not suppress epileptiform discharges during electrocorticography unlike most other anesthetic agents.[3,4]

We have used dexmedetomidine extensively as part of our anesthesia technique during both awake and asleep surgeries for resection of epileptic foci in patients with medically intractable seizures. On the basis of our clinical experience, patients undergoing awake surgeries for resection of epileptic foci require higher doses of dexmedetomidine to achieve adequate sedation compared with the doses required for the patients undergoing other awake neurosurgical procedures, such as for brain tumor resection. This clinical observation may be explained by differences in either the pharmacokinetic

What We Already Know about This Topic

- Dexmedetomidine is used as part of an anesthetic technique for resection of epileptic foci in patients with intractable seizures
- Anticonvulsant medications, such as phenytoin and carbamazepine, are potent inducers of cytochrome P450 drug–metabolizing enzymes

What This Article Tells Us That Is New

- The elimination clearance of dexmedetomidine was increased by 43% in subjects with seizure disorders taking phenytoin or carbamazepine
- Patients taking phenytoin or carbamazepine may require higher than normal maintenance doses of dexmedetomidine to maintain the desired level of sedation/anesthesia

Submitted for publication May 13, 2013. Accepted for publication December 11, 2013. From the Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia, Vancouver, British Columbia, Canada (A.M.F.); Drug Metabolism and Pharmacokinetics, Genentech Inc., San Francisco, California (H.W.); Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada (K.W.R.); and Department of Neurology (T.S., P.A.G.), Department of Anesthesia and Perioperative Care (S.V., P.O.T.), University of California San Francisco, San Francisco, California.

 Anesthesiology 2014; 120:1118-25

or pharmacodynamic profile of dexmedetomidine in the epileptic population.

The pharmacokinetic profile of dexmedetomidine may be altered in patients taking antiepileptic medications. Dexmedetomidine undergoes extensive biotransformation by the liver and the cytochrome P450 enzyme complex, and patients with liver dysfunction have decreased clearance of dexmedetomidine.[5,6] Because anticonvulsants such as phenytoin and carbamazepine are potent inducers of P450 enzymes, patients taking these medications may exhibit increased clearance of dexmedetomidine. Anticonvulsants are known to interact with many other drugs through this mechanism.[7] Conversely, patients with seizure disorders may have alterations in their pharmacodynamic response to dexmedetomidine. Seizure activity activates the sympathetic nervous system and may result in persistent autonomic dysregulation.[8] As dexmedetomidine is a sympatholytic drug, it is possible that seizure disorders may impact the pharmacodynamic profile of dexmedetomidine.

Neither the pharmacokinetics nor pharmacodynamics of dexmedetomidine has been investigated in patients with seizure disorders taking anticonvulsant drugs. Our objective was to compare the pharmacokinetic and pharmacodynamic profile of dexmedetomidine between healthy volunteers and volunteers receiving enzyme-inducing anticonvulsant medications.

Materials and Methods

This study was conducted after obtaining approval from the Institutional Review Board of the University of California San Francisco (approved on September 15, 2010) and was performed with written informed consent from all volunteer subjects (ClinicalTrials.gov identifier NCT01116700). The study was conducted under a Federal Drug Administration Investigational New Drug Application (109627).

Study Population

We enrolled a total of 16 volunteers between the ages of 18 and 45 yr. The seizure group (eight subjects) included patients with a history of seizures who were taking P450 enzyme–inducing anticonvulsant medication (phenytoin or carbamazepine). The control group was comprised of eight volunteers of similar age and weight. We excluded individuals who had any of (1) a history of cardiac, hepatic, or renal disease; (2) a history of alcohol or drug abuse; or (3) greater than 130% of ideal body weight. Volunteers in the control group taking any prescription medications other than oral contraceptives were excluded. All volunteers were fully fasted and asked to abstain from alcohol and coffee for 24 h before the study day.

Study Protocol

During the 6-h study period, all subjects rested supine on a padded operating room table, in a quiet, temperature-controlled study room and were covered with blankets during the study. On the morning on the study, a peripheral intravenous catheter was inserted to administer fluid and dexmedetomidine (Precedex®; Abbott Laboratories, Abbott Park, IL). Lactated Ringer's solution was administered at a rate of approximately 200 ml/h during the first hour of the study (during the dexmedetomidine infusion), and at 50 ml/h thereafter until the study was completed. With local anesthetic infiltration, a cannula was placed into the radial artery to permit continuous measurement of arterial blood pressure and intermittent arterial blood sampling. Subjects were monitored with continuous electrocardiography and pulse oximetry on the distal phalanx of an index finger (LNCS Adtx-3 Spo_2 Sensor; Masimo Corp., Irvine, CA). An acoustic respiration sensor (RAS-125; Masimo Corp.) was placed on the subject's neck to permit continuous respiratory rate monitoring. After cleaning the skin of the forehead with an alcohol swab and slightly abrading the skin, an entropy sensor (GE Entropy Sensor; GE Healthcare, Helsinki, Finland) was placed on left forehead as recommended by the manufacturer for processed electroencephalography and facial electromyography monitoring.

After all monitors were applied, subjects rested for 10 to 15 min followed by the intravenous administration of dexmedetomidine in four progressively increasing intravenous target-controlled doses. A computer-controlled infusion pump (Harvard Apparatus 22; Harvard Apparatus, South Natick, MA) was used to infuse dexmedetomidine (1 μg/ml) to target plasma concentrations of 0.3, 0.6, 1.2, and 2.4 ng/ml. The duration of each infusion step was 15 min. The pump was controlled by STANPUMP software, which adjusted and recorded the rate of infusion every 10 s, based on available pharmacokinetic data for dexmedetomidine (*i.e.*, a central volume of distribution of 0.427 l/kg and elimination and distributional rate constants of k10 = 0.0212 min^{-1}, k12 = 0.0744 min^{-1}, and k21 = 0.0264 min^{-1}). The target plasma concentrations were selected based on previous studies and to ensure a wide range of sedation.[9,10]

Pharmacodynamic Data

The study flow chart is illustrated in figure 1. The escalating target-controlled infusion steps were designed to provide a range of dexmedetomidine concentrations to characterize the pharmacodynamic profile (sedation) of dexmedetomidine. We assumed that any potential difference in rate of dexmedetomidine elimination would have a minimal effect on dexmedetomidine plasma levels during the 15-min target-controlled infusion steps. Sedation was measured using both objective and subjective measures of sedation. Subjects were assigned sedation scores using the Ramsay Sedation Scale (RSS) and Observer's Assessment of Alertness/Sedation (OAA/S) Scale followed by a subjective assessment of sedation using a Visual Analog Scale (VAS). The RSS is a six-point scale (1, patient is anxious and agitated or restless or both; 2, patient is cooperative, orientated, and tranquil; 3, patients responds to commands only; 4, brisk response

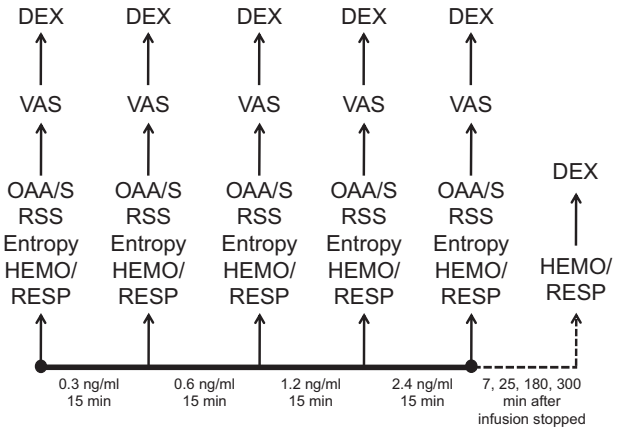

Fig. 1. Study flow chart illustrating the timeline for dexmedetomidine infusion and data collection. Data were recorded in the following order: hemodynamic (HEMO) and respiratory (RESP) data, entropy data, Ramsay Sedation Scale (RSS), Observer's Assessment of Alertness/Sedation (OAA/S) Scale after which the patients were asked for a Visual Analog Scale (VAS) score, and last an arterial blood sample was drawn to determine the plasma concentration of dexmedetomidine (DEX).

to a light glabellar tap or auditory stimulus; 5, sluggish response to a light glabellar tap or auditory stimulus; and 6, no response to a light glabellar tap or auditory stimulus) and the OAA/S is a five-point composite assessment of responsiveness, speech, facial expression, and eyes (five least sedated and one completely sedated).[11,12] Subjects were asked to provide a score on a VAS to determine their level of sedation (0 = completely awake to 10 = cannot stay awake). A VAS score of 10 was assigned if the subject was unresponsive.

Response entropy (RE) and state entropy (SE) were monitored continuously using Datex-Ohmeda S/5 Anesthesia Monitor with an Entropy Module (Datex-Ohmeda; GE Healthcare).

Pharmacokinetic Data

Five milliliter of arterial blood samples were collected using the intra-arterial cannula at baseline, the end of each dexmedetomidine infusion step, and 7, 25, 180, and 300 min after the end of the dexmedetomidine infusion. Blood samples were immediately placed on ice and plasma was subsequently separated in a refrigerated centrifuge. Plasma samples were stored at −70°C until analysis.

The dexmedetomidine assay was performed by Dr. Mika Scheinin, M.D., Ph.D., Department of Pharmacology, Drug Development and Therapeutics, University of Turku, Turku, Finland. The analysis method for the determination of concentrations of dexmedetomidine was modified from previous reports.[13,14] Concentrations of dexmedetomidine (reference standard: dexmedetomidine hydrochloride, Fermion Oy, Oulu, Finland) in human EDTA plasma were determined with high-performance liquid chromatography tandem mass spectrometry after solid-phase extraction with Sep-Pak®tC18 96-well extraction plates (Waters Co., Milford, MA) with $^{2}H_{6}$-medetomidine (ORM-14385; Orion Pharma, Espoo, Finland) as an internal standard. The sorbent was activated with methanol and stabilized with water before pipetting the plasma samples, mixed 1:7 with 0.1% formic acid, into the wells. Elution was with 1 ml of a mixture of methanol and acetonitrile (1:1, v/v). The extract was evaporated with nitrogen and the residue was dissolved in 0.05 ml of the mobile-phase solvent. Separation was performed with a Gemini® column (2 × 150 mm, 5 μm; Phenomenex, Torrance, CA) with isocratic flow (0.3 ml/min) of a mobile phase consisting of two parts of 0.1% formic acid in water and one part of a mixture of methanol and acetonitrile (1:1, v/v). Quantitative detection was performed in multireaction monitoring mode with a triple quadrupole mass spectrometer (API 4000; MDS Sciex, Concord, Ontario, Canada). For dexmedetomidine and the internal standard, the precursor ions (m/z) were 201.2 and 208.2. The precursor ion m/z 208.2 was selected from the ion pattern of deuterated dexmedetomidine. The fragment ions (m/z) monitored and used for quantitation were 95.1 for dexmedetomidine and 97.1 for the internal standard. The chromatograms were processed using Applied Biosystems/MDS Sciex software (Analyst 1.4.1; Concord, Ontario, Canada). Calibration standards with eight nonzero concentrations and quality control samples with three different concentration levels (low, medium, and high) were included in all assays. Calibration standards and quality controls were prepared in drug-free human EDTA acid plasma. The linear concentration range was from 0.02 to 10.0 ng/ml. The interassay accuracies of the quality control samples (0.03, 0.9, and 8.0 ng/ml) were 89, 89, and 101.5%, respectively. This assay has a lower limit of detection of 20 pg/ml and coefficient of variation of 5.7% in the relevant concentration range.

Hemodynamic and Respiratory Data

Systolic and diastolic blood pressures and heart rate were monitored continuously using Datex-Ohmeda S/5 Anesthesia Monitor with E-PRESTN hemodynamic module (Datex-Ohmeda; GE Healthcare). Percent oxygen saturation and respiratory rate were recorded continuously using a Rad-87 Pulse oximeter (Masimo Corp.) and an acoustic respiration sensor (RAS-125; Masimo Corp.). Hemodynamic and respiratory data were recorded at each time point before the pharmacodynamic assessments and blood sampling (fig. 1).

Pharmacokinetic Analysis

We used a standard two-stage approach to compare population parameters between healthy volunteers and volunteers on anticonvulsant medications. For our pharmacokinetic analysis, we chose to use a two-compartment model as prior experience by us[15] and others[16,17] has found it adequate to describe the pharmacokinetics of dexmedetomidine. The dexmedetomidine dose was entered into the pharmacokinetic model as four separate infusion steps consisting of a

Table 1. Subject Characteristics in the Control and Seizure Groups

	Control (N = 8)	Seizure (N = 8)
Male, % (n)	62.5 (5/8)	50 (4/8)
Age, yr (median, range)	26.5 (20–40)	28.5 (20–41)
Height, cm (median, range)	175 (155–190)	170 (120–183)
Weight, kg (median, range)	75 (50–92)	73 (56–97)

cumulative dose applied over the infusion interval. Four infusion steps were required as the infusion rate of each step differed. A two-compartment model was fit to individual plasma concentration–time data using SAAMII v1.2.1 (Saam Institute, University of Washington, Seattle, WA). This fit to the two-compartment model was performed using the Bayesian estimation feature in SAAMII. Pharmacokinetic parameters from our previous analysis were used as the prior in the Bayesian estimation.[15] This involved estimation of each individual's individual pharmacokinetic parameters followed by calculation of mean and variance of each group and exploration of relationships between covariates and parameters.[18] Mean parameter estimates are presented as the estimate followed by the standard deviation (SD). Student *t* tests were used to determine differences in the pharmacokinetic parameters derived for each group. Relationships between pharmacokinetic parameters and weight were determined using a Pearson correlation coefficient. Student *t* tests and correlation analyses were performed using GraphPad Prism V4.02 (GraphPad Software Inc., San Diego, CA).

Statistical Analysis

A sample size of eight subjects per group was chosen based on previous, similar studies on dexmedetomidine in which the pharmacokinetic parameters were derived from small volunteer populations.[15,19,20] We used a repeated-measures two-factor ANOVA to determine both the effect of dexmedetomidine on measures of sedation (RSS, OAA/S, VAS, RE, and SE) within the groups at different timepoints and differences in sedation scores between the two groups over time during the infusion steps. If a significant difference was found using repeated-measures ANOVA, we performed between-group comparisons with a Student *t* test and within-subject comparisons using a paired *t* test and finally a Bonferroni correction to adjust for multiple comparisons. A similar analysis was used to determine the effect of dexmedetomidine on the hemodynamic and respiratory measures and differences between the two groups. All statistical tests were two-tailed and a *P* value of less than 0.05 was considered statistically significant. The analysis of pharmacodynamic, hemodynamic, and respiratory data was performed using STATA 12.1 (StataCorp, College Station, TX).

Results

All 16 subjects completed the study and were included in the analysis. The two groups were similar with respect to age, weight, height, and sex (table 1). Two subjects in the seizure group were taking phenytoin at total doses of 460 and 800 mg daily. Six subjects were taking carbamazepine (median total daily dose, 1,000 mg; range, 800–1,600 mg). All seizure subjects had been taking carbamazepine or phenytoin for a minimum of 3 months. In the seizure group, five patients were taking additional medications. One patient was taking levetiracetam, two patients were taking lacosamide, one was taking zonisamide and lacosamide, and one patient was also taking losartan, propranolol, ranitidine, and topiramate.

Total cumulative dexmedetomidine doses were 0.27, 0.68, 1.4, and 2.8 μg/kg at the end of the 0.3, 0.6, 1.2, and 2.4 ng/ml target plasma dexmedetomidine steps, respectively. Measured plasma dexmedetomidine concentrations were consistently higher than the predicted plasma concentrations during the target-controlled infusions but not after discontinuation of the infusion (table 2). There were no significant differences in the measured dexmedetomidine plasma levels between the control and seizure groups during the target-controlled infusion steps.

Pharmacokinetics

A total of 144 plasma samples from 16 individuals were included in the population pharmacokinetic analysis. The dexmedetomidine plasma concentration *versus* time data for both study groups is provided in figure 2. The data were best described using a two-compartment model. With the exception of plasma clearance, all pharmacokinetic parameters were similar between the seizure and control groups (table 3). Plasma clearance was significantly higher in the seizure group compared with the control group at 42.7 and 29.9 l/h, respectively (difference of –12.8 l/h; 95% CI, –21.5 to –4.0; $P = 0.007$).

Weight showed a weak but significant correlation with the volume of distribution of the central and peripheral compartments on data pooled from both groups of patients ($r = 0.37$, $P = 0.012$ and $r = 0.46$, $P = 0.004$, respectively)

Table 2. Actual Plasma Concentrations of Dexmedetomidine during and after a Target-controlled Infusion of Dexmedetomidine

Group	TCI 0.3 ng/ml	TCI 0.6 ng/ml	TCI 1.2 ng/ml	TCI 2.4 ng/ml	7-min Postinfusion	25-min Postinfusion	180-min Postinfusion	300-min Postinfusion
Control	0.52 (0.08)	1.02 (0.14)	2.22 (0.43)	4.87 (1.15)	2.46 (0.69)	1.55 (0.39)	0.61 (0.23)	0.39 (0.19)
Seizure	0.50 (0.10)	1.04 (0.25)	2.03 (0.32)	4.56 (0.60)	2.08 (0.34)	1.28 (0.27)	0.35 (0.12)	0.19 (0.09)

All results are reported as mean (SD).
TCI = target-controlled infusion.

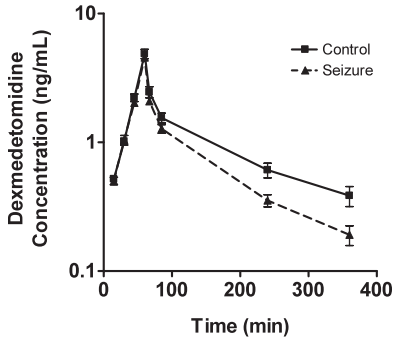

Fig. 2. Observed mean dexmedetomidine plasma concentration *versus* time plot for control and seizure groups. The *squares* (connected by a *solid line*) and *triangles* (connected by a *dashed line*) represent observed mean (±SEM) dexmedetomidine concentrations in control and seizure groups, respectively.

but not with plasma clearance or distributional clearance ($r = 0.021$, $P = 0.94$ and $r = 0.035$, $P = 0.90$, respectively).

Pharmacodynamics

Pharmacodynamic results are shown in table 4. Baseline VAS, RSS, and OAA/S scores did not differ between the groups. Sedation increased significantly (VAS, RSS, and OAA/S scores) in both groups compared with baseline with increasing dexmedetomidine doses during the target-controlled infusion steps. Two control group subjects and three seizure group subjects were unarousable at the end of the 2.4 ng/ml dexmedetomidine plasma target level. There were no significant differences in the OAA/S, RSS, or VAS scores between the seizure and control groups (table 4).

There were no differences in baseline SE or RE values between the groups. SE and RE values decreased significantly in both groups compared with baseline with increasing dexmedetomidine doses during the target-controlled infusion steps (table 4). SE values were lower in the seizure group compared with the control group ($P = 0.029$) (table 4). However, the *post hoc* Student *t* test with correction for multiple comparisons did not find significant differences between the two groups for any of the dexmedetomidine infusion steps. The baseline electroencephalography of one subject in the seizure group had significant amount of slow-wave activity. This subject had baseline RE and SE values of 39 and 28, respectively.

Hemodynamic and Respiratory Data

There were no differences in baseline hemodynamic or respiratory variable values between the groups. Systolic and diastolic blood pressures, heart rate, percent oxygen saturation, and respiratory rate did not differ between the two groups at any time point (table 5). No vasoactive medications were administered. Although several subjects snored while sedated, none of the percent oxygen saturation values declined less than 90%. None of the respiratory rates were less than 8 breaths/min during the study.

Discussion

Our data show that plasma clearance of dexmedetomidine is increased by 43% in subjects with seizure disorders taking enzyme-inducing anticonvulsant medications as compared with healthy control subjects. Although the pharmacokinetic interactions of enzyme-inducing anticonvulsants with other medications such as neuromuscular blockers have long been recognized,[21–23] this effect has not been described with dexmedetomidine. In contrast, dexmedetomidine pharmacodynamics (sedation) did not differ between subjects taking enzyme-inducing anticonvulsant medications and healthy control subjects exposed to similar plasma concentrations of dexmedetomidine. Overall, the increased clearance of dexmedetomidine observed in the seizure group may explain our clinical observations that higher dexmedetomidine infusion rates are required in patients taking enzyme-inducing anticonvulsants. By using the pharmacokinetic parameters derived from our study population, we simulated plasma concentrations of dexmedetomidine after a loading dose of 1 μg/kg over 10 min and at an infusion rate of 1 $\mu g\ kg^{-1}\ h^{-1}$ for 5 h (fig. 3). An increase in the infusion rate by 30% would be required in seizure subjects to achieve similar plasma concentrations to control subjects. The results of the simulation are consistent with our clinical experience.

The pharmacokinetic parameters derived in our control group are consistent with those published previously. Plasma clearance of dexmedetomidine in Korean subjects (33.7 l/h) and in another study of healthy male volunteers (26.7 l/h) was comparable with that in our control subjects (29.9 l/h).[17,19] In comparison, plasma clearance in our volunteers taking enzyme-inducing anticonvulsants was 42.7 l/h. In contrast to previously published dexmedetomidine pharmacokinetic values, weight correlated significantly with the central and

Table 3. Pharmacokinetic Parameters of Dexmedetomidine in Control and Seizure Groups

Pharmacokinetic Parameter	Control (N = 8)	Seizure (N = 8)	*P* Value*	Difference (95% CI)
Plasma clearance (Cl) (l/h)	29.9 (8.9)	42.7 (7.3)	0.007	12.8 (21.5–4.0)
Distributional clearance (Cl_d) (l/h)	77.4 (25.5)	67.2 (13.0)	0.33	–10.2 (–11.6 to 31.9)
Central compartment (V_1) (l)	21.1 (6.7)	22.5 (4.2)	0.62	1.4 (–7.4 to 4.6)
Peripheral compartment (V_2) (l)	65.3 (10.7)	61.3 (10.0)	0.44	–4 (–7.0 to 15.1)

All values shown are mean (SD).

*Using a Student two-sample *t* test to compare control and seizure groups.

Table 4. OAA/S Score, RSS Score, VAS Score, and Entropy Values during a Step-wise Target-controlled Infusion of Dexmedetomidine in Healthy Controls and Seizure Subjects

Group	0 min (Baseline)	15 min (TCI 0.3 ng/ml)	30 min (TCI 0.6 ng/ml)	45 min (TCI 1.2 ng/ml)	60 min (TCI 2.4 ng/ml)	*P* Value†
OAA/S (1–5)						
Control	5 (5–5)	4 (3–5)*	3.5 (3–4)*	2.5 (2–4)*	2 (1–3)*	0.53
Seizure	5 (5–5)	4.5 (4–5)	3.5 (3–4)*	3 (2–4)*	2 (1–3)*	
RSS (1–6)						
Control	2 (2–2)	2 (2–5)	4.5 (4–5)*	5 (4–5)*	5 (5–6)*	0.78
Seizure	2 (2–2)	2 (2–4)	4 (3–5)*	5 (3–5)*	5 (5–6)*	
VAS (0–10)						
Control	0.5 (0–3)	6 (3–8)*	7 (5–9)*	8.5 (8–9)*	10 (8–10)*	0.17
Seizure	1.5 (0–3)	4.5 (1–7)	6.5 (3–10)*	7.5 (6–10)*	10 (6–10)*	
Response entropy (0–100)						
Control	97.5 (97–99)	94 (58–98)	60.5 (26–95)*	26.5 (14–85)*	23 (11–29)*	0.055
Seizure	96 (39–99)	65.5 (33–97)	41.5 (17–66)*	22 (17–44)*	19 (9–32)*	
State entropy (0–91)						
Control	88 (85–91)	84 (45–89)	53 (25–82)*	24 (13–77)*	20 (10–26)*	0.029
Seizure	85 (28–89)	57.5 (25–87)	32.5 (16–52)*	21 (17–40)*	17.5 (9–31)*	

All values shown are median (range).

* $P < 0.05$ compared with baseline using paired *t* tests with a Bonferroni correction for multiple (4) comparisons. † *P* value for comparison between seizure and control groups over time using repeated-measures ANOVA.

OAA/S = Observer's Assessment of Alertness/Sedation; RSS = Ramsay Sedation Scale; TCI = target-controlled infusion; VAS = Visual Analog Scale.

peripheral volumes of distribution in our study although the clinical significance of this finding is unclear.[10,16,17]

The increased elimination of dexmedetomidine among patients receiving anticonvulsant medications may be explained by a clinically significant cytochrome P450–mediated drug–drug interaction. Carbamazepine and phenytoin are known to be potent inducers of multiple P450 enzymes as well as uridine 5'-diphospho-glucoronosyltransferase and epoxide hydrolase.[7,24] Although some of the seizure subjects were taking additional medications, none are known to induce the cytochrome P450 enzyme complex. Dexmedetomidine undergoes extensive glucuronidation and hydroxylation in the liver with minimal excretion of unchanged drug. P450 enzymes implicated in the biotransformation

Table 5. Blood Pressure, Heart Rate, Percent Oxygen Saturation, and Respiratory Rate during and after a Step-wise Target-controlled Infusion of Dexmedetomidine in the Control and Seizure Groups

Group	0 min (Baseline)	15 min (TCI 0.3 ng/ml)	30 min (TCI 0.6 ng/ml)	45 min (TCI 1.2 ng/ml)	60 min (TCI 2.4 ng/ml)	7-min Postinfusion	25-min Postinfusion	180-min Postinfusion	300-min Postinfusion	*P* Value†
Systolic blood pressure										
Control	134 (9)	113 (12)*	104 (8)*	113 (13)*	129 (11)	117 (12)	112 (11)*	103 (7)*	112 (9)*	0.92
Seizure	131 (5)	114 (6)	106 (6)*	111 (15)	127 (19)	116 (21)	108 (18)*	101 (11)*	117 (8)	
Diastolic blood pressure										
Control	69 (6)	60 (6)	58 (8)	64 (7)	77 (10)	69 (9)	65 (9)	55 (9)*	60 (6)	0.15
Seizure	69 (6)	61 (6)	58 (3)	61 (9)	72 (9)	66 (9)	59 (9)	54 (8)*	63 (6)	
Heart rate										
Control	64 (8)	60 (5)	56 (5)	54 (7)	51 (10)*	55 (8)	54 (7)	53 (6)	57 (8)	0.42
Seizure	67 (10)	66 (10)	62 (9)	61 (8)	57 (7)	60 (8)	60 (9)	60 (10)	67 (9)	
Percent oxygen saturation										
Control	99 (1)	98 (1)	98 (1)*	98 (1)	98 (1)	98 (1)*	98 (1)	98 (1)	99 (1)	0.93
Seizure	98 (1)	97 (1)	97 (1)	97 (1)	98 (2)	97 (1)	97 (1)	98 (2)	98 (2)	
Respiratory rate										
Control	12 (5)	13 (4)	14 (3)	14 (2)	15 (2)	15 (3)	14 (3)	12 (2)	13 (2)	0.31
Seizure	14 (2)	11 (2)	13 (1)	14 (2)	15 (2)	15 (2)	14 (2)	13 (2)	13 (1)	

There were no significant differences between the two groups. The shaded column represents the termination of the target-controlled infusion of dexmedetomidine. All values shown are mean (SD).

* $P < 0.05$ compared with baseline using paired *t* tests with a Bonferroni correction for multiple (8) comparisons. † *P* value for comparison between seizure and control groups over time using repeated-measures ANOVA.

TCI = target-controlled infusion.

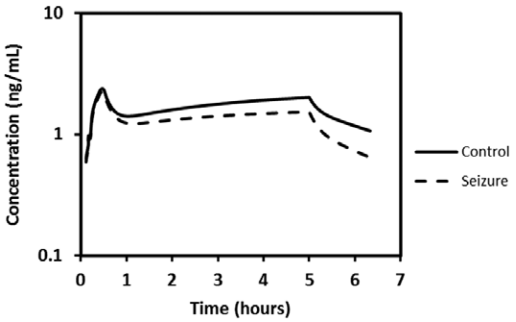

Fig. 3. Simulation of dexmedetomidine plasma concentrations after a loading dose of 1 μg/kg over 10 min followed by an infusion rate of 1 μg kg^{-1} h^{-1} for 5 h in control (*solid line*) and seizure (*dashed line*) subjects.

of dexmedetomidine include CYP2A6 (predominantly), CYP1A1, CYP 2E1, CYP2D6, and CYP2C19.[6] Our study results are consistent with a hypothesis that enzyme induction caused by anticonvulsant medications such as phenytoin and carbamazepine could result in an increased metabolic clearance of dexmedetomidine.

The pharmacokinetic dexmedetomidine data set used for the target-controlled infusion in this study resulted in higher-than-predicted plasma dexmedetomidine concentrations. Although the measured concentrations have exceeded the predicted concentrations of dexmedetomidine during target-controlled infusions in previous studies,[2,15] our data demonstrated a consistently higher overshoot that we did not expect and cannot explain. We chose to use this dexmedetomidine pharmacokinetic data set because of our previous experience with the sedation levels and hemodynamic responses associated with this protocol. For the pharmacodynamic part of the study, we chose four plasma target dexmedetomidine concentrations that would provide us with a wide range of sedation. We achieved our targeted sedation levels that ranged from minimal to deep sedation. At the end of the first dexmedetomidine infusion step, the subjects became slightly sedated, but remained easily arousable. At the highest sedation level, four of our volunteers were unarousable and the rest required significant verbal and tactile stimulation to be aroused.

Similarly, the duration of each infusion step used in the study allowed us to examine pharmacodynamic differences between the two groups. We chose to use 15-min dexmedetomidine infusion steps to have enough time to reach a stable level of sedation at each step, while minimizing the effect of potential differences in dexmedetomidine clearance on plasma dexmedetomidine concentrations. We achieved similar plasma dexmedetomidine concentrations between the two study groups during the four dexmedetomidine infusion steps, allowing for a direct comparison of the pharmacodynamic parameters between the groups.

Our study did not demonstrate a difference in sedation between the two groups as measured by the OAA/S, RSS, and VAS sedation scores during a controlled range of target plasma concentrations. Thus, our results make it unlikely that resistance to sedation with dexmedetomidine in patients with epilepsy is due to altered pharmacodynamics. Our results may be difficult to extrapolate to the clinical setting because our subjects were sedated in a quiet study room without noxious stimuli. Higher dexmedetomidine concentrations are likely needed to achieve equivalent levels of sedation in the typical surgical setting. Finally, our study was designed to detect differences in dexmedetomidine pharmacokinetic parameters between the groups and, thus, may be underpowered to detect differences in other variables.

We included entropy measurements as an objective surrogate measure of sedation. Entropy values declined consistently with increasing dexmedetomidine doses in all subjects. At the highest dexmedetomidine dose level in most subjects, entropy values decreased into the low 20s and this was consistent with clinically observed deep sedation. RE values did not differ between the groups. Although ANOVA showed a potential difference (P = 0.046) in SE values between the groups, our *post hoc* test did not find differences between the groups at any time point. One of the subject's RE and SE data in the seizure groups were a clear outlier. This volunteer had unusual slow-wave electroencephalography activity that resulted in very low RE and SE values at baseline and during sedation. It is possible that the underlying electroencephalography abnormalities associated with refractory epilepsy do not allow a reliable estimation of sedation using existing algorithms.

The hemodynamic and respiratory responses to dexmedetomidine exhibited by our study subjects were consistent with previous reports.[2,19,25] As typically observed with administration of dexmedetomidine, blood pressure initially decreased at low plasma dexmedetomidine concentrations but then increased back to baseline values at higher plasma dexmedetomidine levels, and then decreased again after discontinuation of the infusion.[25] Despite significant levels of sedation, we did not observe arterial hemoglobin desaturation or apneic events also consistent with previous studies.[2,25]

Our study has limitations. Our small sample size and number of data points may have limited the precision of our pharmacodynamic analyses. Two of the scores of sedation (OAA/S and RSS) were assigned by unblinded investigators and may have introduced bias. Although we demonstrated an increased clearance of dexmedetomidine in patients taking enzyme-inducing anticonvulsants, we did not specifically prove that these anticonvulsants caused the increased clearance. Furthermore, we cannot make inferences regarding potential effects of anticonvulsants other than carbamazepine or phenytoin on the pharmacokinetic profile of dexmedetomidine.

Conclusion

Our study demonstrates that patients with seizure disorders taking the enzyme-inducing anticonvulsant medications have increased clearance of dexmedetomidine as compared with healthy control subjects. These findings

account for our clinical impression and hypothesis that this patient population requires higher-than-normal dosing of dexmedetomidine. In contrast, the objective and subjective measures of sedation were similar between the two groups during a controlled range of target plasma concentrations, suggesting that the difference in sedation is related to altered pharmacokinetics, rather than pharmacodynamics. Further studies would be useful to clarify the clinical significance of our findings.

Acknowledgments

The authors gratefully thank Penny Brasher, Ph.D., Vancouver Coastal Health Research Institute, Vancouver, British Columbia, Canada, for her statistical advice and review of the article.

This study was funded by an investigator-initiated grant-in-aid from Hospira, Inc. (Lake Forest, Illinois). Hospira, Inc., was not involved in any aspect of study design, data collection, data analysis, or article preparation.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Flexman: Department of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia, Vancouver General Hospital, Room 2449, JPP 899, West 12th Avenue, Vancouver, British Columbia, Canada V5Z 1M9. alana.flexman@vch.ca.

References

1. Correa-Sales C, Rabin BC, Maze M: A hypnotic response to dexmedetomidine, an α 2 agonist, is mediated in the locus coeruleus in rats. ANESTHESIOLOGY 1992; 76:948–52
2. Hsu YW, Cortinez LI, Robertson KM, Keifer JC, Sum-Ping ST, Moretti EW, Young CC, Wright DR, Macleod DB, Somma J: Dexmedetomidine pharmacodynamics: Part I: Crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. ANESTHESIOLOGY 2004; 101:1066–76
3. Souter MJ, Rozet I, Ojemann JG, Souter KJ, Holmes MD, Lee L, Lam AM: Dexmedetomidine sedation during awake craniotomy for seizure resection: Effects on electrocorticography. J Neurosurg Anesthesiol 2007; 19:38–44
4. Talke P, Stapelfeldt C, Garcia P: Dexmedetomidine does not reduce epileptiform discharges in adults with epilepsy. J Neurosurg Anesthesiol 2007; 19:195–9
5. Rodrigues AD, Roberts EM: The *in vitro* interaction of dexmedetomidine with human liver microsomal cytochrome P4502D6 (CYP2D6). Drug Metab Dispos 1997; 25:651–5
6. Karol MD, Maze M: Pharmacokinetics and interaction pharmacodynamics of dexmedetomidine in humans. Best Pract Res Clin Anaesthesiol 2000; 14:261–9
7. Perucca E: Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol 2006; 61:246–55
8. Parikh S, Gupta A: Autonomic dysfunction in epilepsy and mitochondrial diseases. Semin Pediatr Neurol 2013; 20:31–4
9. Snapir A, Talke P, Posti J, Huiku M, Kentala E, Scheinin M: Effects of nitric oxide synthase inhibition on dexmedetomidine-induced vasoconstriction in healthy human volunteers. Br J Anaesth 2009; 102:38–46
10. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C: Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. ANESTHESIOLOGY 1997; 87:835–41
11. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
12. Ramsay MA, Savege TM, Simpson BR, Goodwin R: Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2:656–9
13. Ji QC, Zhou JY, Gonzales RJ, Gage EM, El-Shourbagy TA: Simultaneous quantitation of dexmedetomidine and glucuronide metabolites (G-Dex-1 and G-Dex-2) in human plasma utilizing liquid chromatography with tandem mass spectrometric detection. Rapid Commun Mass Spectrom 2004; 18:1753–60
14. Snapir A, Posti J, Kentala E, Koskenvuo J, Sundell J, Tuunanen H, Hakala K, Scheinin H, Knuuti J, Scheinin M: Effects of low and high plasma concentrations of dexmedetomidine on myocardial perfusion and cardiac function in healthy male subjects. ANESTHESIOLOGY 2006; 105:902–10
15. Talke P, Richardson CA, Scheinin M, Fisher DM: Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. Anesth Analg 1997; 85:1136–42
16. Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen JP, Scheinin M, Schwilden H, Schüttler J, Olkkola KT: Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth 2012; 108:460–8
17. Lee S, Kim BH, Lim K, Stalker D, Wisemandle W, Shin SG, Jang IJ, Yu KS: Pharmacokinetics and pharmacodynamics of intravenous dexmedetomidine in healthy Korean subjects. J Clin Pharm Ther 2012; 37:698–703
18. Sheiner LB, Beal SL: Evaluation of methods for estimating population pharmacokinetic parameters. II. Biexponential model and experimental pharmacokinetic data. J Pharmacokinet Biopharm 1981; 9:635–51
19. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL: The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. ANESTHESIOLOGY 1993; 78:813–20
20. De Wolf AM, Fragen RJ, Avram MJ, Fitzgerald PC, Rahimi-Danesh F: The pharmacokinetics of dexmedetomidine in volunteers with severe renal impairment. Anesth Analg 2001; 93:1205–9
21. Spacek A, Neiger FX, Krenn CG, Hoerauf K, Kress HG: Rocuronium-induced neuromuscular block is affected by chronic carbamazepine therapy. ANESTHESIOLOGY 1999; 90:109–12
22. Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Ayala M: Rocuronium-induced neuromuscular blockade is affected by chronic phenytoin therapy. J Neurosurg Anesthesiol 2001; 13:79–82
23. Koenig HM, Hoffman WE: The effect of anticonvulsant therapy on two doses of rocuronium-induced neuromuscular blockade. J Neurosurg Anesthesiol 1999; 11:86–9
24. Lynch T, Price A: The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician 2007; 76:391–6
25. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD: The effects of increasing plasma concentrations of dexmedetomidine in humans. ANESTHESIOLOGY 2000; 93:382–94