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Reversal of the Sedative and Sympatholytic Effects of Dexmedetomidine with a Specific α_2-Adrenoceptor Antagonist Atipamezole

A Pharmacodynamic and Kinetic Study in Healthy Volunteers

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Background: **Specific and selective α_2-adrenergic drugs are widely exploited in veterinary anesthesiology. Because α_2-agonists are also being introduced to human practice, the authors studied reversal of a clinically relevant dexmedetomidine dose with atipamezole, an α_2-antagonist, in healthy persons.**

Methods: **The study consisted of two parts. In an open dose-finding study (part 1), the intravenous dose of atipamezole to reverse the sedative effects of 2.5 μg/kg of dexmedetomidine given intramuscularly was determined (n = 6). Part 2 was a placebo-controlled, double-blinded, randomized cross-over study in which three doses of atipamezole (15, 50, and 150 μg/kg given intravenously in 2 min) or saline were administered 1 h after dexmedetomidine at 1-week intervals (n = 8). Subjective vigilance and anxiety, psychomotor performance, hemodynamics, and saliva secretion were determined, and plasma catecholamines and serum drug concentrations were measured for 7 h.**

Results: **The mean ± SD atipamezole dose needed in part 1 was 104 ± 44 μg/kg. In part 2, dexmedetomidine induced clear impairments of vigilance and psychomotor performance that were dose dependently reversed by atipamezole ($P < 0.001$). Complete resolution of sedation was evident after the highest (150 μg/kg) dose, and the degree of vigilance remained high for 7 h. Atipamezole dose dependently reversed the reductions in blood pressure ($P < 0.001$) and heart rate ($P = 0.009$). Changes in saliva secretion and plasma catecholamines were similarly biphasic (*i.e.*, they decreased after dexmedetomidine followed by dose-dependent restoration after atipamezole). Plasma norepinephrine levels were, however, increased considerably after the 150 μg/kg dose of atipamezole. The pharmacokinetics of atipamezole were linear, and elimination half-lives for both drugs were approximately 2 h. Atipamezole did not affect the disposition of dexmedetomidine. One person had symptomatic sinus arrest, and another had transient bradycardia approximately 3 h after receiving dexmedetomidine.**

Conclusions: **The sedative and sympatholytic effects of intramuscular dexmedetomidine were dose dependently antagonized by intravenous atipamezole. The applied infusion rate (75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for the highest atipamezole dose was, however, too fast, as evident by transient sympathoactivation. Similar elimination half-lives of these two drugs are a clear advantage considering the possible clinical applications. (Key words: Antidote; receptors; sympathomimetics).**

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α_2-ADRENOCEPTOR agonists such as clonidine and more recently dexmedetomidine induce sedation, reduce anesthetic requirements, and improve perioperative hemodynamic and sympathoadrenal stability.[1] Dexmedetomidine is being evaluated as an adjunct to anesthesia. Compared with clonidine, dexmedetomidine is approximately 10 times more selective toward the α_2-adrenoceptor and acts as a full agonist in some pharmacologic test models in which the former displays only partial agonism.[2,3]

The pharmacokinetic and pharmacodynamic profile of intramuscularly administered dexmedetomidine may

be suited to its proposed clinical use as a preanesthetic sedative and anxiolytic or as an anesthetic adjunct.[4] The 2.5 μg/kg intramuscular dose of dexmedetomidine has been studied most widely in the clinical setting and seems to possess comparable sedative and anxiolytic properties to 0.07 to 0.08 mg/kg of midazolam, with additional effectiveness during surgery.[5–9]

The sedative and cardiovascular effects after intramuscular administration of dexmedetomidine may last longer than is optimal for short-duration surgical procedures.[10] A specific antidote could be beneficial in clinical situations in which the α_2-adrenoceptor agonist effects need to be reversed. Indeed, atipamezole, a highly specific and selective α_2-adrenoceptor antagonist,[11–14] has been shown to reverse rapidly and effectively the cardiovascular and sedative effects of intravenous dexmedetomidine in humans.[15] This concept is already being applied widely in veterinary practice.[16]

The four objectives of the current study were (1) to determine an effective single dose of intravenous atipamezole to reverse the pharmacologic effects induced by dexmedetomidine 2.5 μg/kg given intramuscularly; (2) to assess the possible reappearance of dexmedetomidine-induced effects after the initial reversal; (3) to find possible pharmacokinetic interactions; and (4) to study the tolerability and safety of this drug combination.

Materials and Methods

Volunteers and Study Design

Fourteen healthy, nonsmoking men (age, 20–28 yr; weight, 65–88 kg; height, 167–186 cm) were studied after they gave written informed consent. The general health of the volunteers was determined by detailed examinations, including laboratory screening. None of the volunteers was receiving long-term drug therapy or had received any medication for at least 2 days before the study. The study protocol was approved by the Ethics Committee of Turku University Hospital and submitted to the Finnish National Board of Health.

This phase 1 study consisted of two parts: (1) an open dose-finding portion (part 1) in which the intravenous dose of atipamezole needed to reverse the sedative effects of 2.5 μg/kg dexmedetomidine given intramuscularly was determined in six volunteers; and (2) a placebo-controlled, double-blinded, and multiple cross-over study (part 2) in which three doses of atipamezole (*i.e.*, 15, 50, and 150 μg/kg) and saline were administered in random order to eight men after dexmedetomidine (2.5 μg/kg) was given intramuscularly. The atipamezole doses were selected based on results obtained in part 1. The washout period between treatments was at least 7 days. Randomization was performed using Latin squares balanced for possible carryover effects.

Study Procedure

The volunteers fasted overnight and were instructed to abstain from using alcohol for 48 h before the study sessions. The sessions started at 8 AM and when the volunteers arrived in the study laboratory, two intravenous cannulas, one for drug (atipamezole or placebo) administration and the other for blood sampling, were inserted. The men were connected to electrocardiograph and blood pressure devices. A rest period lasting at least 30 min was permitted before baseline measurements were obtained. A standard lunch was served 4 h after dexmedetomidine administration. Until and after the lunch, the volunteers rested in a semireclined or supine position.

Each session began with baseline measurements of vigilance, anxiety, psychomotor performance, saliva secretion (in part 2 only), systolic and diastolic blood pressure, and heart rate (HR). Baseline blood samples for chemical determinations were also drawn. Subsequently, 2.5 μg/kg dexmedetomidine hydrochloride (Orion Pharma R&D, Turku, Finland) was injected into the vastus lateralis muscle. One hour after dexmedetomidine administration, atipamezole hydrochloride (Orion Pharma R&D) was administered intravenously, and volunteer monitoring and measurements continued for an additional 6 h (table 1).

In part 1, the volunteers were told that the first drug (dexmedetomidine) induces sedation and that they would very likely fall asleep. They were also told that they would receive an infusion of the antagonist (atipamezole 12.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) approximately 1 h later and would be asked to report when they no longer felt sedated. At this point, the atipamezole infusion was stopped and the exact duration of the infusion (to calculate the dose) was recorded.

In part 2, exactly 1 h after administration of dexmedetomidine, three doses of atipamezole (15, 50, and 150 μg/kg) and placebo were infused in 2 min in a total volume of 20 ml. These doses (*i.e.*, one tenth, one third, and the entire apparent "wake-up dose") were selected based on results from part 1 (see Results).

Table 1. Schedule of Study Measurements*

Part 1

	Activities			
				Blood Sample
Time (min)	VAS	DSST	BP, HR	Drugs
−45				
Arrival of subject, cannulations, instructions				
−30				
Stabilization				
−1 (= baseline)	X	X	X	X
Dexmedetomidine injection (0)				
15				X
30	X		X	X
60	X	X	X	X
Atipamezole infusion (start at 63–66)				
End of atipamezole infusion	X		X	X
80	X		X	X
100	X		X	X
120	X	X	X	X
150	X		X	X
180	X	X	X	X
210	X		X	X
240	X	X	X	X
Lunch				
300	X	X	X	X
360	X	X	X	X
420	X	X	X	X

Part 2

	Activities					
					Blood samples	
Time (min)	VAS	DSST	Saliva	BP, HR	Drugs	CATAM
−45						
Arrival of subject, cannulations, instructions						
−30						
Stabilization						
−1 (= baseline)	X	X	X	X	X	X
Dexmedetomidine injection (0)						
15					X	
30	X			X	X	
55	X	X	X	X	X	X
Atipamezole injection (60–62)						
65	X			X		
75	X			X	X	X
90	X			X	X	X
120	X	X	X	X	X	
180	X	X	X	X	X	X
240	X	X	X	X	X	
Lunch						
300	X	X		X	X	X
360	X	X	X	X	X	
420	X	X	X	X	X	X

VAS = visual analogue scales; DSST = Digit Symbol Substitution Test; Saliva = saliva secretion; BP = blood pressure measurement; HR = heart rate measurement; Drugs = drug concentrations in serum; CATAM = plasma catecholamines.

* Because dexmedetomidine-induced effects were assessed at 60 min in Part 1, atipamezole infusion was started at 63–66 min. In Part 2 measurements were made at 55 min enabling atipamezole dosing exactly 60 min after dexmedetomidine.

Assessment Methods

The time points for the different measurements and blood samples were modified slightly after part 1 and are shown in table 1. The degree of vigilance and anxiety was assessed subjectively by horizontal ungraded 100 mm visual analog scales (VAS). The pairs of extremes (0–100) were defined as drowsy–alert (vigilance) and calm–nervous (anxiety). Psychomotor performance was assessed using the Digit Symbol Substitution Test. In this test, the volunteers were asked to replace symbols with numbers within a limited time, and then the number of replaced symbols (total and correct) was calculated.[17] Standard preprinted test sheets were used. In addition, basal (nonstimulated) saliva secretion was measured in part 2. Dental cotton rolls were placed at the orifices of parotid ducts on both sides and under the tongue for 1 min and then discarded. These were replaced by preweighed rolls that were left in place for 2 min and then weighed again.

Electric activity of the heart (lead V5) was monitored throughout the sessions. Systolic and diastolic blood pressures and HR were recorded noninvasively using an automated device (Nippon Colin 203 Y or 103 N, Tokyo, Japan). In addition, the occurrence of all adverse events was rigorously sought and recorded.

Chemical Determinations

In part 2, 5 ml venous blood samples were drawn into prechilled tubes containing K_2 ethylene diamine tetraacetic acid. The samples were placed on ice and centrifuged promptly, and the plasma was separated and frozen in −70°C until it was analyzed. Norepinephrine, epinephrine, and 3,4-dihydroxyphenylglycol (DHPG, a metabolite of norepinephrine) concentrations were determined using high-performance liquid chromatography with coulometric detection.[18]

To analyze the concentrations of dexmedetomidine and atipamezole in serum, 10 ml venous blood was drawn in both parts of the study. The blood samples were centrifuged, and the separated sera were stored in plastic tubes at −20°C until they were analyzed. The analyses were performed using validated gas chromatographic mass spectrometric methods.[4,19] The lower limit of quantitation was 0.1 ng/ml for dexmedetomidine and 0.05 ng/ml for atipamezole.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic parameters were calculated by standard methods: Peak concentration (C_{max}) was taken as the maximum measured concentration in serum, and time to peak concentration (t_{max}) was taken as the sampling time at which peak concentration was observed. The area under the serum concentration–time curve was calculated using the linear trapezoidal rule to the last non-zero concentration and extrapolated to infinity. The terminal half-life ($t_{½}$) was calculated by the ln2 per elimination rate constant, which was determined by unweighed linear least-squares regression analysis from the linear portion of the log concentration–time data using the software package BIOPAK (SCI Software, Lexington, KY).

Statistical Analysis

In part 1, only descriptive statistics were performed. Results in part 2 were analyzed using analysis of variance for repeated measurements using the MIXED PROCEDURE of SAS 6.12 statistical software (SAS Institute, Cary, NC). Separate analyses were performed for the time intervals 0 to 55 min (dexmedetomidine period) and 55 to 420 min (atipamezole period). The first time interval was analyzed to ensure that the effects of dexmedetomidine did not vary among the four sessions. The following terms were included in the models: treatment, time, period, carryover (in the atipamezole period), treatment–time interaction, and period–time interaction. When a significant treatment–time interaction was detected, the comparison between each active treatment *versus* placebo for changes from the first time point to different time points was performed by linear contrasts. When a significant treatment effect was detected, paired comparisons between treatment main effects were performed. Differences in the pharmacokinetic parameters were determined using analysis of variance. Statistical analyses were performed at a two-sided 0.05 significance level. The data are presented as mean ± SD unless specified otherwise.

Results

Efficacy

Part 1. Dexmedetomidine (2.5 μg/kg given intramuscularly) decreased the mean ± SD VAS score for vigilance from 48 ± 26 at baseline to 19 ± 13 at 60 min. All the volunteers fell asleep but were easily awakened for the assessments. The mean ± SD atipamezole dose needed to reverse this sedative effect was 104 ± 44 μg/kg. The lowest and highest individual doses were 50 and 163 μg/kg, with corresponding infusion times of 4 and 13 min, respectively. At the end of the atipamezole

Table 2. Summary of Overall Statistical Analyses (Analysis of Variance for Repeated Measurements) in the Double-blind Part of the Study (n = 8)

		Dexmedetomidine Period			Atipamezole Period		
Variable		Factor 1 (treatment)	Factor 2 (time)	Interaction	Factor 1 (treatment)	Factor 2 (time)	Interaction
Vigilance	F	0.12	50.60	1.64	16.24	24.47	8.69
	P	0.95	<0.001	0.17	<0.001	<0.001	<0.001
Anxiety	F	0.95	3.95	0.72	1.86	5.26	1.57
	P	0.44	0.044	0.64	0.18	<0.001	0.046
DSST	F	2.86	23.54	4.57	4.27	19.72	3.36
	P	0.066	0.0019	0.015	0.023	<0.001	<0.001
SBP	F	0.14	52.45	0.61	21.36	6.91	4.26
	P	0.93	<0.001	0.72	<0.001	<0.001	<0.001
DBP	F	0.58	35.65	0.91	14.02	5.47	3.35
	P	0.64	<0.001	0.50	<0.001	<0.001	<0.001
HR	F	0.41	7.19	0.66	1.91	8.78	1.87
	P	0.75	0.0071	0.68	0.17	<0.001	0.0094
Saliva	F	1.70	29.58	1.50	7.61	12.56	8.17
	P	0.19	<0.001	0.23	0.0025	<0.001	<0.001
Norepinephrine	F	0.82	23.74	1.98	12.75	21.34	14.84
	P	0.50	0.0018	0.15	<0.001	<0.001	<0.001
Epinephrine	F	1.00	12.20	1.07	2.58	6.19	1.89
	P	0.42	0.010	0.39	0.091	<0.001	0.034
DHPG	F	1.12	20.26	4.17	12.43	16.92	10.90
	P	0.37	0.0028	0.021	<0.001	<0.001	<0.001

Dexmedetomidine period = time intervals 0–55 min; Atipamezole period = 55–420 min (see fig. 1 for exact measurement points); DSST = Digit Symbol Substitution Test; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; saliva = saliva secretion; DHPG = 3,4-dihydroxyphenylglycol.

infusion, the average VAS ratings were above baseline (*i.e.*, 71 ± 15), where they remained until the end of the session. Dexmedetomidine-induced decrease in VAS score for anxiety was less evident (from 31 ± 26 at baseline to 20 ± 15 at 60 min), and atipamezole increased the rating to a maximum of 50 ± 11 at 80 min. No evident drug-induced changes in the Digit Symbol Substitution Test were observed. Dexmedetomidine induced 8–13% average reductions in systolic and diastolic blood pressures and HR, which were restored immediately after atipamezole infusion. Based on these results, 15, 50, and 150 μg/kg doses of atipamezole were selected for part 2.

Part 2. Dexmedetomidine (2.5 μg/kg given intramuscularly) decreased VAS scores for vigilance similarly (79–85%) in all four sessions (table 2). Sedation was dose dependently ($P < 0.001$, overall analysis of variance) reversed by atipamezole (fig. 1). Complete resolution of sedation was evident after the highest dose (150 μg/kg), and the VAS scores remained high until the end of the study. Significant differences compared with placebo were also observed in the 50 μg/kg ($P = 0.048$) and 150 μg/kg ($P < 0.001$) treatment sessions but not in the 15 μg/kg session ($P = 0.054$). In addition, the difference between the two highest doses was significant ($P = 0.003$). When contrasts at individual time points were analyzed, significant differences compared with placebo were seen between 75 and 90 min, 65 and 180 min, and 65 and 240 min in the 15, 50, and 150 μg/kg dose levels, respectively.

Dexmedetomidine induced a decrease (48–60%) in VAS score for anxiety (table 2). The VAS decrease was reversed by atipamezole, and an approximately 100% increase from baseline was seen in the 150 μg/kg session (fig. 1). The overall treatment–time interaction was significant ($P = 0.046$, table 2), and analyses of contrasts at 65–120 min revealed significant differences only between placebo and the 150-μg/kg session.

Dexmedetomidine decreased the Digit Symbol Substitution Test scores in all four sessions (table 2). In the 15 μg/kg treatment session, the number of replaced symbols was, however, affected most (table 2, fig. 2). The average number of replaced symbols was increased from 36 in the first session to 42–44 in the other three, suggesting learning during the study ($P < 0.001$ for period effect). In the postatipamezole analysis, a significant treatment–time interaction ($P < 0.001$) was revealed. In paired overall comparisons, only the 150 μg/kg dose differed significantly ($P = 0.019$) from pla-

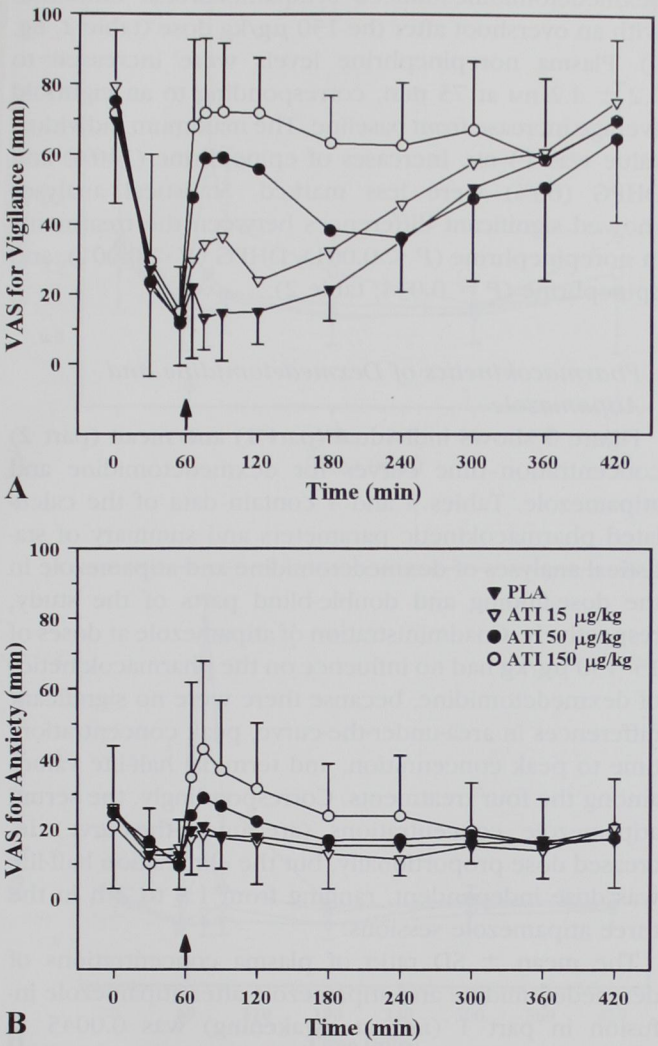


Fig. 1. The mean (SD) visual analog scale ratings for (*A*) vigilance and (*B*) anxiety in part 2 of the study (n = 8). Dexmedetomidine (2.5 μg/kg) was administered intramuscularly at time 0 followed by intravenous placebo or atipamezole (15, 50, and 150 μg/kg) infusion at 60–62 min (indicated by an arrow). Most error bars have been omitted for clarity.

cebo. Analysis for correct substitutions gave identical results (data not shown).

Significant reductions in systolic (12–15%) and diastolic (11–17%) blood pressures and HR (7–13%) were observed after dexmedetomidine administration (table 2). Atipamezole dose dependently restored these changes, and slight overshoots were seen at 65 or 75 min in the 150 μg/kg session (fig. 3). No relapse in blood pressure reduction was seen after the highest dose of atipamezole, whereas a second nadir was evident in HR at 120 min (*i.e.*, approximately 1 h after atipamezole administration). Overall statistical analyses showed significant differences in systolic ($P < 0.001$) and diastolic ($P < 0.001$) blood pressures between the treatments. In paired analyses, the highest dose differed significantly from placebo ($P < 0.001$ for both) and other doses of atipamezole. In the HR analysis, only the treatment–time interaction was significant ($P = 0.009$), and the only significant contrast compared with placebo was at 75 min in the 150 μg/kg treatment session.

Dexmedetomidine-induced reduction (78–83%) in saliva secretion was reversed completely by the 150 μg/kg dose, only marginally by the 50 μg/kg dose, whereas no

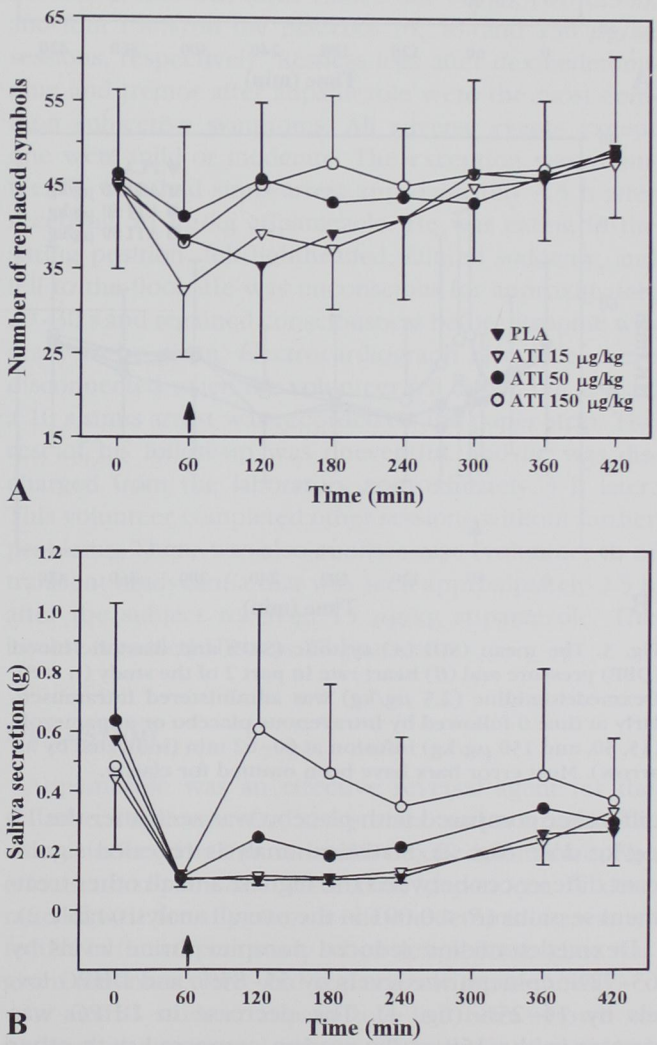


Fig. 2. The mean (SD) number of replaced symbols in the (*A*) Digit Symbol Substitution Test and (*B*) saliva secretion in part 2 of the study (n = 8). Dexmedetomidine (2.5 μg/kg) was administered intramuscularly at time 0 followed by intravenous placebo or atipamezole (15, 50, and 150 μg/kg) infusion at 60–62 min (indicated by an arrow). Most error bars have been omitted for clarity.

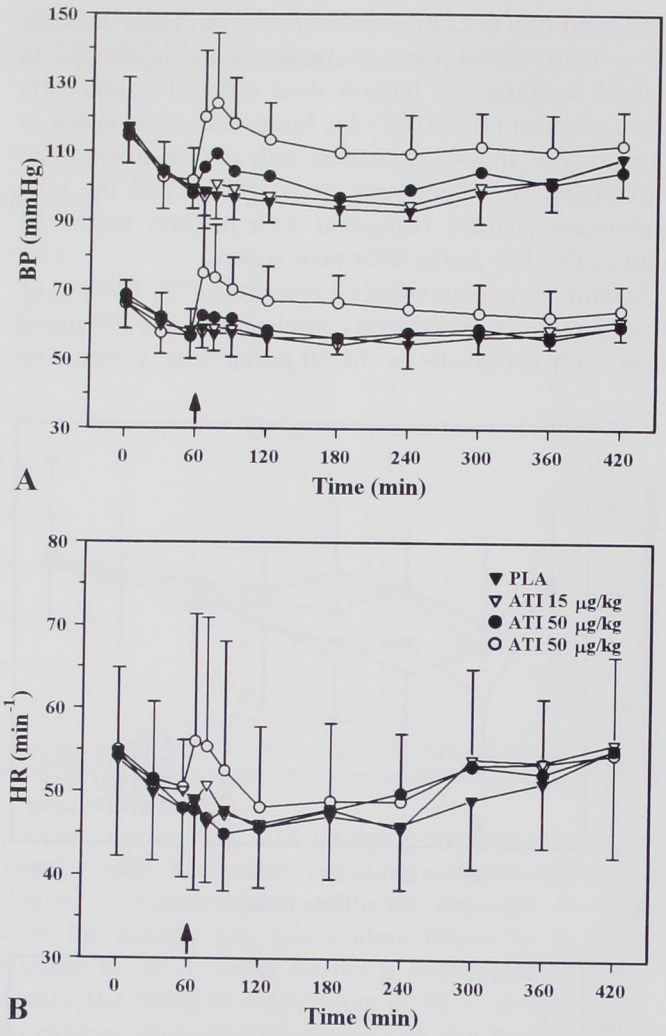


Fig. 3. The mean (SD) (*A*) systolic (SBP) and diastolic blood (DBP) pressure and (*B*) heart rate in part 2 of the study (n = 8). Dexmedetomidine (2.5 μg/kg) was administered intramuscularly at time 0 followed by intravenous placebo or atipamezole (15, 50, and 150 μg/kg) infusion at 60–62 min (indicated by an arrow). Most error bars have been omitted for clarity.

difference compared with placebo was seen after the 15 μg/kg dose (fig. 2). Statistical analysis revealed significant differences between the highest and all other treatment sessions ($P < 0.001$ in the overall analysis, table 2).

Dexmedetomidine reduced norepinephrine levels by 63–72%, epinephrine levels by 55–85%, and DHPG levels by 14–25% (fig. 4). The decrease in DHPG was greater in the 150 μg/kg session compared with other treatment sessions ($P = 0.021$, table 2). There were also significant period effects in the norepinephrine ($P < 0.001$ for period-time interaction) and epinephrine ($P = 0.026$) analyses before atipamezole administration. Nevertheless, atipamezole dose dependently reversed dexmedetomidine-induced sympathoadrenal inhibition with an overshoot after the 150 μg/kg dose (table 2, fig. 4). Plasma norepinephrine levels were increased to 7.2 ± 4.2 nM at 75 min, corresponding to an eightfold average increase from baseline. The maximum individual value was 13 nM. Increases of epinephrine (140%) and DHPG (60%) were less marked. Statistical analyses showed significant differences between the treatments in norepinephrine ($P < 0.001$), DHPG ($P < 0.001$), and epinephrine ($P = 0.034$; table 2).

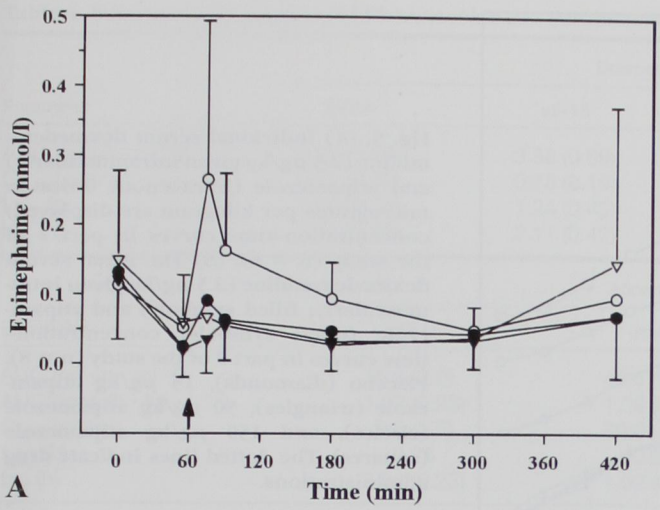
Pharmacokinetics of Dexmedetomidine and Atipamezole

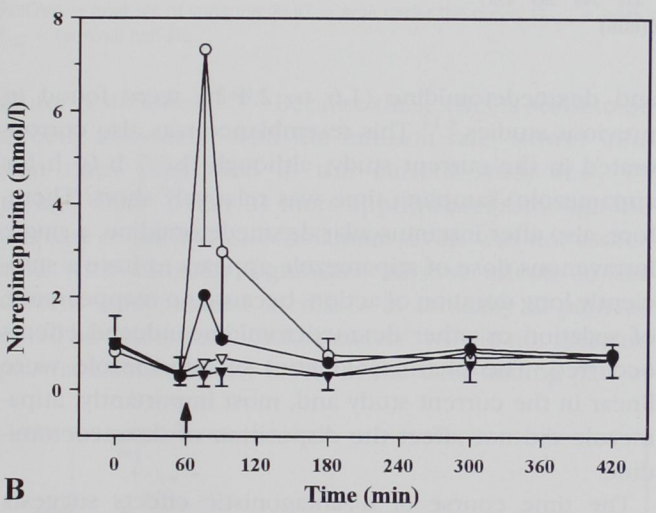
Figure 5 shows individual (part 1) and mean (part 2) concentration–time curves for dexmedetomidine and atipamezole. Tables 3 and 4 contain data of the calculated pharmacokinetic parameters and summary of statistical analyses of dexmedetomidine and atipamezole in the dose-finding and double-blind parts of the study, respectively. Coadministration of atipamezole at doses of 15–150 μg/kg had no influence on the pharmacokinetics of dexmedetomidine, because there were no significant differences in area-under-the-curve, peak concentration, time to peak concenration, and terminal half-life values among the four treatments. Correspondingly, the serum atipamezole concentrations (area-under-the-curve) increased dose proportionally, but the elimination half-life was dose independent, ranging from 1.8 to 2 h in the three atipamezole sessions.

The mean ± SD ratio of plasma concentrations of dexmedetomidine and atipamezole after atipamezole infusion in part 1 (*i.e.*, at awakening) was 0.0045 ± 0.0014. Only as a descriptive measure (nonindependent observations), the correlation of the dexmedetomidine–atipamezole concentration ratio *versus* vigilance was plotted in part 2. Only time points between 75 and 180 min were included because dexmedetomidine-induced sedation began to wear off after 3 h (fig. 1). Dexmedetomidine levels were also relatively stable during this period (fig. 5). A negative trend ($r = -0.54$) was observed (fig. 6).

Safety

In part 1, four volunteers (67%) had at least one adverse event. All of these were moderate and resolved spontaneously. Three men reported dryness of the mouth beginning after dexmedetomidine administration but always before atipamezole administration. One volunteer had sweating of his palms and another had flush-





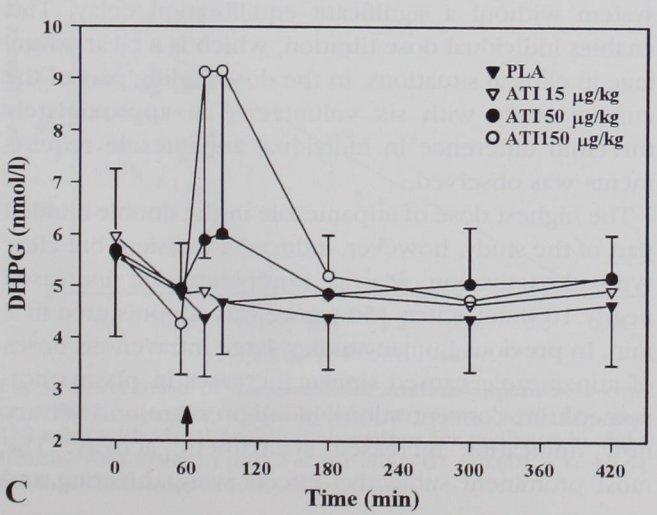


Fig. 4. The mean (SD) levels of (*A*) plasma epinephrine, (*B*) norepinephrine, and (*C*) 3,4-dihydroxyphenylglycol (DHPG) in part 2 of the study (n = 8). Dexmedetomidine (2.5 μg/kg) was administered intramuscularly at time 0 followed by intravenous placebo or atipamezole (15, 50, and 150 μg/kg) infusion at 60–62 min (indicated by an arrow). Most error bars have been omitted for clarity.

ing of his cheeks and palpitation immediately after discontinuing atipamezole infusion.

In part 2, six volunteers (75%) had at least one adverse event during the sessions. The number of men having adverse events was three (38%), one (13%), two (25%), and four (50%) in the placebo, 15, 50, and 150 μg/kg sessions, respectively. Restless legs after dexmedetomidine and tremor after atipamezole were the most common subjective symptoms. All adverse events except one were mild or moderate. The exception was volunteer 7, who had sinus arrest approximately 3.5 h after receiving 50 μg/kg atipamezole. He was eating in the sitting position, felt lightheaded, fainted suddenly, and fell to the floor. He was unconscious for approximately 20–30 s and regained consciousness before atropine was ready to be given. Electrocardiograph electrodes were disconnected when the volunteer fell down, but at least a 10 s sinus arrest was recorded on the paper strip. The rest of his follow-up was uneventful, and he was discharged from the laboratory approximately 3 h later. This volunteer completed other sessions without further problems. There was also another case (volunteer 8) of transient bradycardia that was seen approximately 2.5 h after the subject received 15 μg/kg atipamezole. The lowest recorded HR was 27 beats/min.

Discussion

Atipamezole was an effective reversal agent for the sedative, cardiovascular, xerostomia, and sympatholytic effects induced by intramuscular dexmedetomidine. The effects of atipamezole were dose dependent. A dose ratio of 60:1 for atipamezole–dexmedetomidine was effective in the current study when dexmedetomidine was given intramuscularly and atipamezole intravenously.

In animal studies, atipamezole has been shown to increase the neuronal release of norepinephrine and antagonize the sedative, hypotensive, and hypothermic effects of α_2-adrenoceptor agonists.[11,12] The rapid, almost immediate, awakening of our volunteers from dexmedetomidine-induced sedation after atipamezole corresponds well with previous human experience.

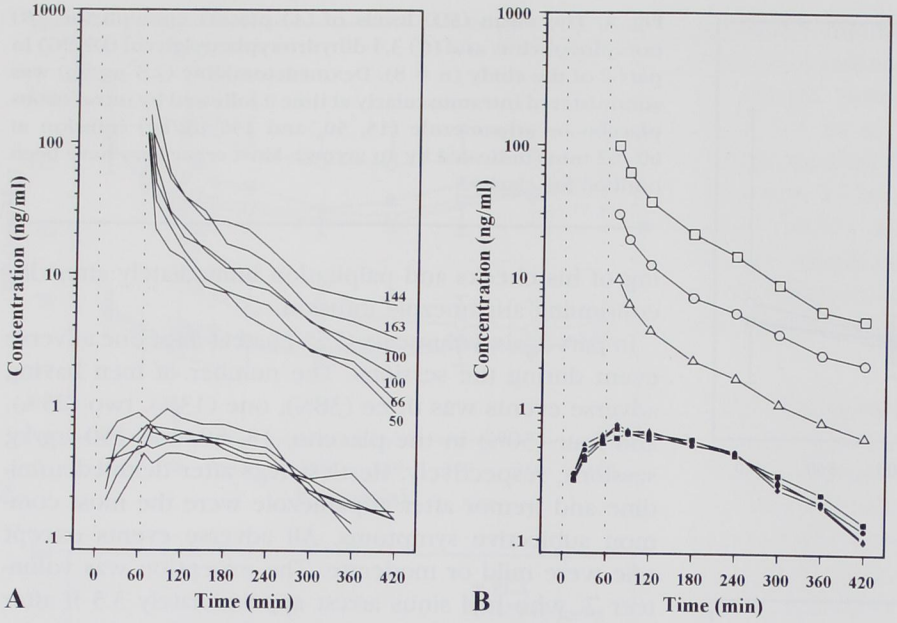


Fig. 5. (*A*) Individual serum dexmedetomidine (2.5 μg/kg given intramuscularly) and atipamezole (intravenous doses in micrograms per kilogram are displayed) concentration–time curves in part 1 of the study (n = 6). (*B*) The mean serum dexmedetomidine (2.5 μg/kg given intramuscularly; filled symbols) and atipamezole (open symbols) concentration–time curves in part 2 of the sutdy (n = 8). Placebo (diamonds), 15 μg/kg atipamezole (triangles), 50 μg/kg atipamezole (circles), and 150 μg/kg atipamezole (squares). The dotted lines indicate drug administrations.

Dose ratios ranging from 40:1 to 100:1 were effective when both drugs were given intravenously to a comparable group of six healthy male volunteers.[15] A somewhat lower ratio (25:1) was reported to be effective after minor gynecologic surgery in women who received paracervical blockade supplemented with dexmedetomidine.[20]

The selection of the dexmedetomidine dosage for the current study was based on previous clinical experience. In patients undergoing major surgery during general anesthesia, 2.5 μg/kg given intramuscularly has provided sufficient preoperative sedation and improved intraoperative cardiovascular stability.[5–9] Atipamezole was administered approximately 1 h after dexmedetomidine in the current study (*i.e.*, close to dexmedetomidine's peak effect after intramuscular administration).[4] Relatively similar elimination half-lives of atipamezole (1.5 to 2 h) and dexmedetomidine (1.6 to 2.4 h) were found in previous studies.[4,14] This resemblance was also corroborated in the current study, although the 7 h (6 h for atipamezole) sampling time was relatively short. Therefore, also after intramuscular dexmedetomidine, a single intravenous dose of atipamezole appears to have a sufficiently long duration of action, because no reappearance of sedation or other dexmedetomidine-induced effects occurred. The pharmacokinetics of atipamezole were linear in the current study and, most importantly, atipamezole did not affect the disposition of dexmedetomidine.

Table 3. Summary of Pharmacokinetic Parameters of Dexmedetomidine and Atipamezole in Part 1

Parameter	Dexmedetomidine	Atipamezole
Dose (μg/kg)	2.5	103.8 (43.5)
AUC (ng · h · ml^{-1})	3.08 (0.33)	99.77 (49.24)
AUC/dose (h · kg · L^{-1})	NA	0.96 (0.17)
C_{max} (ng/ml)	0.67 (0.18)	138.5 (37.9)
t_{max} (h)	1.43 (0.33)	NA
$t_{1/2}$ (h)	1.97 (0.71)	1.55 (0.14)

Values are mean (SD), n = 6.

NA = not applicable; AUC = area under the curve; C_{max} = peak concentration (in serum); t_{max} = time to peak concentration; $t_{1/2}$ = terminal half-life.

The time course of α_2-antagonistic effects suggests rapid access of atipamezole into the central nervous system without a significant equilibration delay. This enables individual dose titration, which is a clear advantage in clinical situations. In the dose-finding part of the current study with six volunteers, an approximately threefold difference in individual atipamezole requirements was observed.

The highest dose of atipamezole in the double-blinded part of the study, however, induced a transient but clear sympathoactivation. Plasma norepinephrine increased nearly 10 times when 150 μg/kg was administered in 2 min. In previous human studies, large intravenous doses of atipamezole caused similar increases in plasma norepinephrine concentrations, blood pressure, and salivary flow, indicating increased sympathetic activity. The most prominent subjective effects were shivering and

Table 4. Summary and Analysis of Pharmacokinetic Parameters of Dexmedetomidine and Atipamezole in Part 2

	Dexmedetomidine				ANOVA	
Parameter	Saline	ati-15	ati-50	ati-150	$F_{3,18}$	P
AUC (ng · h · ml^{-1})	3.42 (0.89)	3.38 (0.59)	3.39 (0.77)	3.36 (0.47)	0.01	1.00
C_{max} (ng/ml)	0.71 (0.22)	0.78 (0.19)	0.78 (0.18)	0.81 (0.14)	0.63	0.60
t_{max} (h)	1.39 (0.35)	1.24 (0.43)	1.51 (0.46)	1.33 (0.31)	0.57	0.64
$t_{1/2}$ (h)	2.14 (0.45)	2.11 (0.42)	1.97 (0.47)	1.90 (0.61)	0.48	0.70

	Atipamezole			ANOVA	
Parameter	ati-15	ati-50	ati-150	$F_{2,8}$	P
AUC (ng · h · ml^{-1})	15.6 (3.0)	45.5 (9.0)	141.8 (16.8)	994	<0.0001
AUC/dose (h · kg · L^{-1})	1.02 (0.23)	1.02 (0.31)	0.92 (0.11)	1.34	0.31
C_{max} (ng/ml)	9.5 (1.5)	30.0 (4.6)	98.7 (11.8)	1927	<0.0001
t_{max} (h)	0.25	0.25	0.25	NA	NA
$t_{1/2}$ (h)	2.04 (0.23)	1.92 (0.35)	1.83 (0.23)	2.06	0.19

Data show mean (SD, n = 8) values for the pharmacokinetic parameters of dexmedetomidine and atipamezole for the tested atipamezole doses and ANOVA results (for log-transformed AUC, AUC/dose and C_{max}, and for untransformed t_{max} and $t_{1/2}$).

ANOVA = analysis of variance; AUC = area under the curve; C_{max} = peak concentration (in serum); t_{max} = time to peak concentration; NA = not applicable; $t_{1/2}$ = terminal half-life.

motor restlessness.[13,14] Because these effects seem to be directly associated with the infusion rate, slower infusion rates than used in the current study (*i.e.*, 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$) may be more appropriate. Although the increase in plasma catecholamine levels was not associated with clinically significant adverse effects in the current study, similar increases in critically ill patients could be deleterious. Unfortunately, we did not measure plasma catecholamine levels in the dose-finding part of our study, in which a considerably slower infusion rate (12.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was applied.

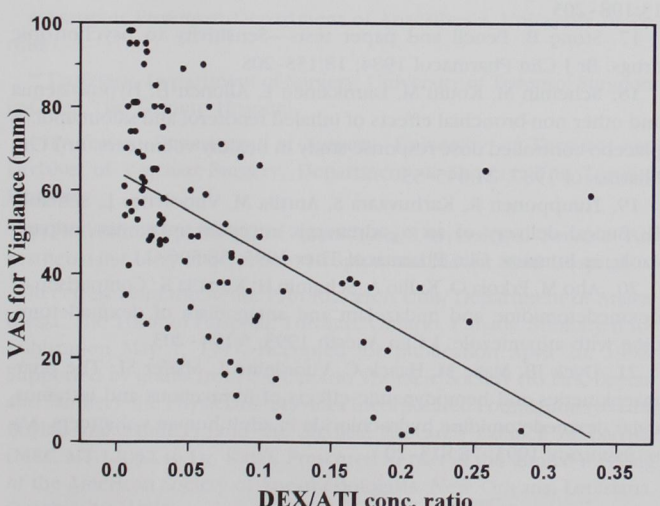


Fig. 6. Correlation of the dexmedetomidine–atipamezole concentration ratio after atipamezole (time points 75, 90, 120, and 180 min) with visual analog scale ratings for vigilance in eight healthy volunteers in part 2 of the study ($P < 0.001$, $r = -0.54$ for these nonindependent observations).

Atipamezole is approved and marketed in several European countries and in the United States as a reversal agent for medetomidine (an α_2-agonist)-induced sedation and analgesia in pet animals. The combined use of dexmedetomidine (the pharmacologically active d-isomer of medetomidine) and atipamezole also could be used in human anesthetic settings, especially if rapid recovery is desirable. Current and previous results from studies of healthy volunteers[15] and patients[20] suggest that this is feasible with these novel α_2-adrenergic drugs. Similar elimination rates must also be considered advantageous in this context. Atipamezole also would constitute a pharmacologically rational antidote in cases of overdose.

Dexmedetomidine can induce bradycardia, and one severe case (transient sinus arrest) was reported in the current study. The episode represented a typical vasovagal collapse, and dexmedetomidine most likely aggravated its development, although the volunteer revealed afterward that he had fainted several times in the past, such as while donating blood. α_2-Adrenoceptor activation can attenuate the physiologic response (*i.e.*, sympathetic activation) associated with changing to an upright posture, leading to a severe orthostatic reaction. A few cases of vasovagal collapse or sinus arrest also have been reported after dexmedetomidine administration, particularly in young healthy patients.[21] Because of the physiologic mechanism of action

(decreased release of endogenous transmitter instead of receptor blockade), the responsiveness to anticholinergics, vasopressors, and cardiac stimulants is, however, maintained. Caution with potent α_2-adrenoceptor agonists such as dexmedetomidine is warranted, however, as suggested earlier.[6,8] Dryness of the mouth and restless legs were the most common adverse effects for dexmedetomidine in the current study.

In conclusion, the effects of intramuscular dexmedetomidine were dose dependently reversed by intravenous atipamezole administration. A dose ratio of 60:1 for atipamezole-dexmedetomidine was found to be effective because the 150 μg/kg intravenous dose of atipamezole rapidly and completely reversed the sedative and sympatholytic effects induced by 2.5 μg/kg intramuscular dexmedetomidine. Transient sympathoactivation seen after the highest dose of atipamezole may be avoided by using a slower infusion rate than was applied in the current study. Because of the rapid access of atipamezole into the central nervous system, individual dose titration also is feasible. The combined use of receptor-specific α_2-adrenergic drugs also deserves further exploration in human anesthesiology.

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