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Rapid reversal of α_2-adrenoceptor agonist effects by atipamezole in human volunteers

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1 The ability of atipamezole, a specific and selective α_2-adrenoceptor antagonist, to reverse the pharmacological effects induced by the α_2-adrenoceptor agonist dexmedetomidine was studied in six healthy male volunteers. Each volunteer received in four sessions in a randomized and single-blind manner three different doses (6.7 $\mu g\ kg^{-1}$, 27 $\mu g\ kg^{-1}$ and 67 $\mu g\ kg^{-1}$) of atipamezole or saline placebo as 5 min i.v. infusions preceded by a fixed i.v. dose of dexmedetomidine (0.67 $\mu g\ kg^{-1}$).

2 Dexmedetomidine caused profound sedation, with the subjects actually falling asleep. This was effectively reversed by the two highest doses of atipamezole.

3 Dexmedetomidine reduced salivary flow on average by 70%. A rapid and full reversal of this effect was seen after the highest dose of atipamezole.

4 Hypotension induced by dexmedetomidine was also effectively antagonized by atipamezole. Bradycardia was very modest after dexmedetomidine in this study, and thus no reversal of α_2-adrenoceptor agonist-induced bradycardia could be demonstrated.

5 Plasma noradrenaline concentrations were reduced by 80% by dexmedetomidine. This was effectively antagonized by atipamezole, and the highest dose caused a 50% overshoot in plasma noradrenaline concentrations over the basal levels.

6 It is concluded that the effects of dexmedetomidine are effectively reversible by atipamezole. A dose ratio of 10 : 1 for atipamezole : dexmedetomidine was clearly insufficient for this purpose, but ratios in the range of 40 : 1 to 100 : 1 were found to be effective in the current experimental situation.

Keywords atipamezole α_2-adrenoceptor antagonist dexmedetomidine α_2-adrenoceptor agonist pharmacodynamics

Introduction

The therapeutic uses of α_2-adrenoceptor antagonists are still relatively unexplored. A potential future clinical use for them is reversal of the effects induced by α_2-adrenoceptor agonists.

A new therapeutic application has recently been implicated for clonidine and other α_2-adrenoceptor agonists in anaesthetic practice (Hamilton, 1988; Longnecker, 1987). Clonidine has been shown to reduce halothane anaesthetic requirements in experimental animals (Bloor & Flacke, 1982; Kaukinen & Pyykkö, 1979) and to have beneficial stabilizing haemodynamic effects in coronary bypass surgery (Flacke *et al.*, 1987) and in hypertensive surgical patients (Ghignone *et al.*, 1987). The potent, specific and selective α_2-adrenoceptor agonists medetomidine (Savola *et al.*, 1986; Scheinin *et al.*, 1987a; Virtanen *et al.*, 1988), and especially its active (+)-isomer dexmedetomidine (Kallio *et al.*, 1989) also significantly reduce the anaesthetic requirements in laboratory animals (Vickery *et al.*, 1988) and human patients (Aantaa *et al.*, 1990; Aho *et al.*, 1990). Dexmedetomidine could thus be a useful addition to the drugs currently used in anaesthetic practice.

Atipamezole (MPV-1248) is a novel potent, specific and selective α_2-adrenoceptor antagonist devoid of significant interactions with other neurotransmitter receptors (Virtanen *et al.*, 1989). In animal studies it has been shown to increase the neuronal release of noradrenaline and antagonize the sedative, hypotensive and hypothermic effects of α_2-adrenoceptor agonists

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(Scheinin *et al.*, 1988). In human subjects atipamezole, administered as intravenous infusions, causes an increase in venous plasma noradrenaline concentrations indicating an increased sympathetic activity, blood pressure elevation and an increase in salivary flow. Subjective effects have included anxiety, sweating and coldness of hands and feet, and tremor (Karhuvaara *et al.*, 1989, 1990).

Pharmacological antagonists are widely used in modern anaesthetic practice to terminate the actions of e.g. opiates, muscle relaxants and benzodiazepines. An antidote for the reversal of α_2-adrenoceptor agonist induced effects could be useful after short-lasting surgical procedures, when long duration of the sedative effects is not desirable, or in the treatment of adverse effects or possible overdosage. Previously, the α_2-adrenoceptor antagonist idazoxan has been reported to reverse (Clifford & Price, 1984), and MK-912 to antagonize (Warren *et al.*, 1989) the effects of i.v. clonidine. In the present study we investigated the effectiveness and safety of atipamezole in reversing the hypotensive, bradycardic, sympatholytic and sedative effects of dexmedetomidine in healthy human volunteers.

Methods

Subjects

Six healthy male volunteers (age 22–28 years, height 176–182 cm, weight 64–80 kg) participated after giving written informed consent. They had taken no medications in the month preceding this study. The general health of the volunteers was ascertained by detailed medical history, physical examination, ECG recording and clinical chemistry tests. The study protocol was approved by the local Ethics Committee and the Finnish National Board of Health.

Design of the study

The experiment was carried out as a single-blind, randomized, placebo-controlled cross-over study. Each subject received three single doses (6.7 $\mu g\ kg^{-1}$, 27 $\mu g\ kg^{-1}$ and 67 $\mu g\ kg^{-1}$, or 0.5, 2 and 5 mg for a person weighing 75 kg) of atipamezole and saline placebo as 5 min intravenous infusions 20 min after a standard i.v. dose of 0.67 $\mu g\ kg^{-1}$ dexmedetomidine. Both drugs were supplied by Farmos Group Ltd, Turku, Finland.

Study outline

The subjects arrived at the laboratory early in the morning after fasting overnight. Alcoholic beverages were prohibited 48 h before each session. Two antecubital intravenous cannulae were inserted for blood sampling and drug administration, the subjects were weighed, and were then connected to an ECG monitor. Thereafter, they remained recumbent throughout the study sessions.

The first blood samples and recordings were taken after a minimum of 30 min of supine rest had elapsed from the completion of the preparations. At time zero (0 min) dexmedetomidine (diluted in 5 ml physiological saline) was injected over 5 min. At 20 min atipamezole hydrochloride (diluted in 5 ml), or saline placebo, was administered as an intravenous infusion over 5 min using an infusion pump (Perfusor ED 2, B. Braun, Melsungen, FRG).

Samples of venous blood were collected for determinations of noradrenaline (NA) concentrations in plasma with high performance liquid chromatography (Scheinin *et al.*, 1987b). Blood pressure and heart rate were measured noninvasively with an automated sphygmomanometer (Nippon Colin 203 Y or 103N, Tokyo, Japan). Visual analogue scales were used to estimate subjective drug-induced sedation. The left end of a 100 mm long line represented 'fully alert' and the right end 'profound sedation'. In addition, the subjects were urged to report any effects possibly related to the drugs. The critical flicker fusion (c.f.f.) threshold was determined as an objective measure of sedation (Smith & Misiak, 1976). Saliva secretion was assessed by placing preweighed dental cotton rolls at the orifices of both parotid ducts and under the tongue for two minutes. Collection of blood samples and other measurements were carried out at the time points indicated in Figures 1–5.

Statistical analysis

Analysis of variance (ANOVA) for repeated measurements with two within factors (dose and time) was employed. Separate analyses were performed for the 'pre-atipamezole' and for two or three 'post-atipamezole' periods. The 'pre-atipamezole' (−15–20 min) period was analysed with ANOVA to ensure that the effects of dexmedetomidine did not vary between the four sessions. The arbitrary division of the 'post-atipamezole' period was based on the pilot experiments performed prior to the present placebo-controlled study. The first 'post-atipamezole' period included the last assessments of each variable before atipamezole administration (assessments at 15 or 20 min) and the first few assessments after it (up to 30 or 45 min). In other words, it was the period of the rapid changes induced by atipamezole. The 'post-atipamezole' periods analysed for each individual variable are presented in Table 1.

When significant ($P < 0.05$) main effects of dose, or dose × time interactions, were detected, the analysis was continued further by peforming separate ANOVAs between each dose level. Greenhouse-Geisser adjusted P-values were used if pooled orthogonal components showed non-sphericity (Keselman & Keselman, 1984). The calculations were done with BMDP 4V programs (BMDP Statistical Software Inc., Los Angeles, CA, USA).

Results

Vigilance

Dexmedetomidine caused similar ($P = 0.68$) subjective sedation during all sessions (Figure 1), and the subjects actually fell asleep 10–15 min after the dexmedetomidine injections, but were easily awakened when the VASs

Table 1 Analysis of variance for repeated measurements with two within factors, dose and time. Saline placebo or three doses of atipamezole was infused between 20 and 25 min after dexmedetomidine administration. Time periods analyzed are presented in parentheses.

Variable	Factor 1 = dose	Factor 2 = time	Interaction
Vigilance (VAS)			
(15–45 min)			
F	16.64	87.10	9.90
P	0.00	0.00*	0.00*
(45–240 min)			
F	11.97	21.94	11.43
P	0.00	0.00*	0.00*
C.f.f.			
(15–30 min)			
F	1.40	14.26	2.64
P	0.28	0.01	0.12*
(30–240 min)			
F	2.77	3.00	1.78
P	0.08	0.09*	0.19*
Salivation			
(15–30 min)			
F	8.97	13.86	9.67
P	0.00	0.01	0.01*
(30–240 min)			
F	5.68	3.61	2.14
P	0.01	0.05*	0.12*
Systolic blood pressure			
(20–45 min)			
F	7.06	4.79	4.49
P	0.00	0.02*	0.02*
(45–180 min)			
F	11.63	3.92	1.37
P	0.00	0.06*	0.29*
(180–240 min)			
F	7.92	12.82	3.94
P	0.00	0.00*	0.03*
Diastolic blood pressure			
(20–45 min)			
F	10.85	6.00	4.86
P	0.00	0.03*	0.00*
(45–180 min)			
F	15.30	0.98	1.24
P	0.00	0.42*	0.33*
(180–240 min)			
F	8.54	15.04	1.54
P	0.00	0.00*	0.25*
Heart rate			
(20–45 min)			
F	0.28	3.42	0.69
P	0.84	0.10*	0.79*
(45–180 min)			
F	0.22	2.82	0.81
P	0.88	0.10*	0.52*
(180–240 min)			
F	0.28	0.30	1.60
P	0.84	0.75*	0.24*
Plasma noradrenaline			
(15–30 min)			
F	13.08	26.81	17.54
P	0.00	0.00	0.01*
(30–240 min)			
F	12.15	6.06	2.71
P	0.00	0.03	0.07*

*Greenhouse-Geisser adjusted *P* value

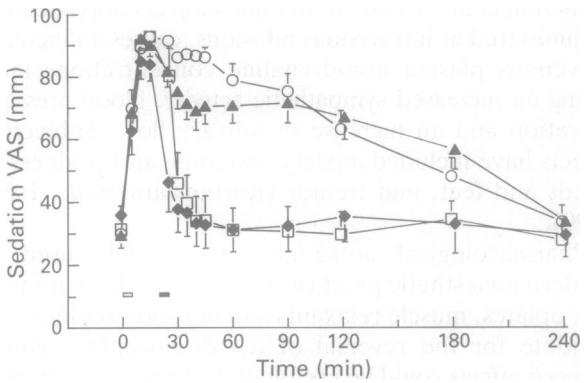

Figure 1 Reversal of dexmedetomidine-induced subjective sedation by atipamezole in six healthy male volunteers. The means ± s.e. mean of scores on a 100 mm long visual analogue scale (VAS), 100 mm representing profound sedation, are presented. Dexmedetomidine (0.67 μg kg^{-1}) was injected intravenously at 0 min. From 20 to 25 min saline placebo (○), or atipamezole at doses of 6.7 μg kg^{-1} (▲), 27 μg kg^{-1} (□) or 67 μg kg^{-1} (◆) was infused intravenously. The horizontal bars (blank for dexmedetomidine and filled for atipamezole) represent the time of the two drug infusions.

were presented or c.f.f. measurements made. After placebo infusion no immediate change was detected in the VAS scores, and the sedation scores only returned to baseline at 240 min. Immediately after the infusion of the lowest dose of atipamezole a small shift, significantly different from placebo (Figure 1, Table 2), occurred in the VAS recordings, but the subjects remained clearly sedated and the VAS scores were clearly above baseline until 240 min (Figure 1). After the intermediate dose (27 μg kg^{-1}) the subjects were still quite sedated immediately after the infusion but opened their eyes soon afterwards, and the VAS readings were almost back to baseline 5 min after the end of the infusion. All subjects opened their eyes already during the infusion of the highest dose of atipamezole. The VAS readings returned to near the baseline already immediately at the end of the infusion (Figure 1), and from 25 min onwards, the VAS scores did not differ from baseline. No rebound sedation was seen after the two highest doses of atipamezole. Pairwise ANOVA revealed statistically significant dose × time interactions between all dose levels, except intermediate and high, in the initial (15–45 min; Tables 1 and 2) as well as in the later (45–240 min; *P* values not shown) 'post-atipamezole' period.

Dexmedetomidine induced a mean reduction of 3 Hz (from 38 to 35 Hz) in c.f.f. threshold during all sessions. This was completely reversed by the highest dose of atipamezole, but overall ANOVA did not reveal statistically significant differences between the treatments (Table 1).

Saliva secretion

Saliva secretion was decreased by approximately 70% by dexmedetomidine during all sessions (Figure 2). The highest atipamezole dose induced full and the intermediate dose partial reversal of this effect, although no statistically significant difference could be demonstrated between these doses. The lowest dose did not significantly differ from placebo (Figure 2, Tables 1 and 2).

Table 2 The dose × time interactions obtained from pairwise analyses of the effects of placebo and three different doses of atipamezole. Analysis of variance with two within factors (dose and time); the data are from the first time period after atipamezole administration including the last assessments before atipamezole infusions (see Table 1).

Variable	*pl* vs *lo*	*pl* vs *int*	*pl* vs *hi*	*lo* vs *int*	*lo* vs *hi*	*int* vs *hi*
Vigilance (VAS)						
F	9.40	17.21	15.15	9.86	6.76	3.85
P	0.00*	0.00*	0.00*	0.00*	0.02*	0.07*
Salivation						
F	2.20	5.48	18.76	6.38	20.09	2.25
P	0.20	0.07	0.01	0.05	0.01	0.19
Systolic BP						
F	1.26	4.20	9.61	2.27	6.50	2.55
P	0.81*	0.04*	0.01*	0.14*	0.03*	0.11*
Diastolic BP						
F	0.22	10.63	11.22	5.79	4.78	0.83
P	0.95*	0.01*	0.00*	0.01*	0.03*	0.48*
Plasma NA						
F	7.48	22.63	19.50	26.03	17.87	10.76
P	0.04	0.01	0.01	0.00	0.01	0.02

*Greenhouse-Geisser adjusted *P* value.
pl = placebo, lo = lowest dose, int = intermediate dose, hi = highest dose of atipamezole.

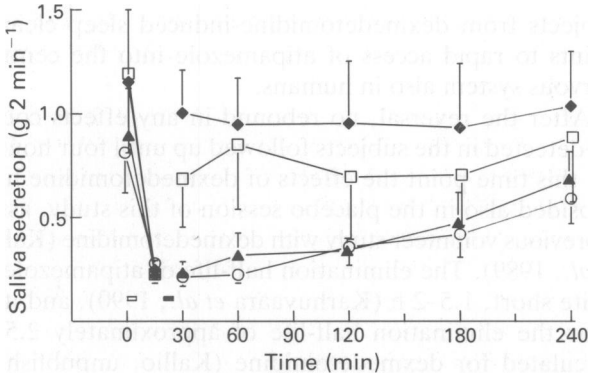

Figure 2 The effect of atipamezole on dexmedetomidine-induced inhibition of salivary flow. Means ± s.e. mean are presented. Symbols as in Figure 1.

Blood pressure and heart rate

After a small initial blood pressure increase, dexmedetomidine lowered both systolic and diastolic blood pressure similarly ($P = 0.30$ and $P = 0.56$, respectively) during all sessions (Figures 3a and b). After placebo and the lowest dose of atipamezole a small further decline was seen in blood pressure up to 60 min, while blood pressure returned near to baseline soon after the infusion of the two higher doses of atipamezole. In the first 'post-atipamezole' period statistically significant differences could be demonstrated between all treatments except placebo and the low dose of atipamezole, and between the two highest doses of atipamezole (Tables 1 and 2, Figures 3a and 3b). In the later period (45–180 min) blood pressure was significantly higher during the high and intermediate dose sessions than during the placebo and low dose sessions.

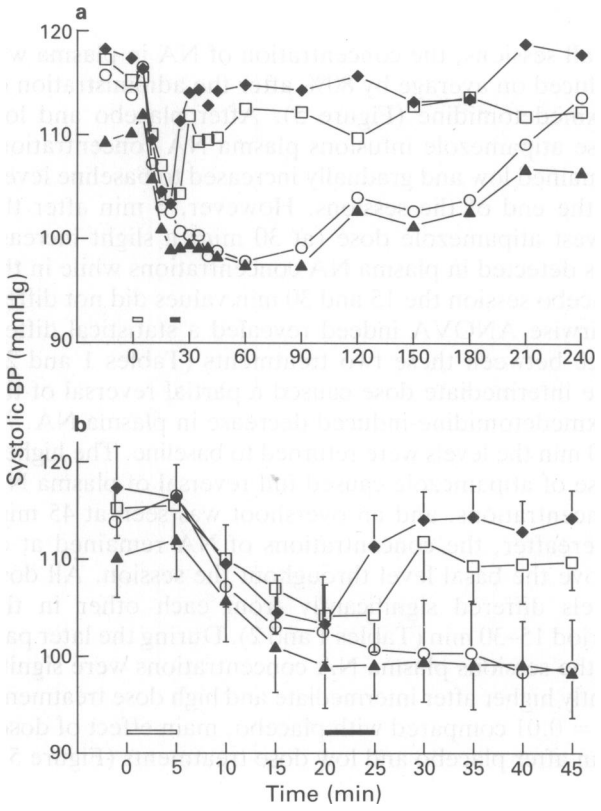

Figure 3 a) Dexmedetomidine-induced reduction of systolic blood pressure and the reversal of this effect by atipamezole. Symbols as in Figure 1, error bars omitted for clarity. b) Expanded time scale for Figure 3a. Means ± s.e. mean are presented.

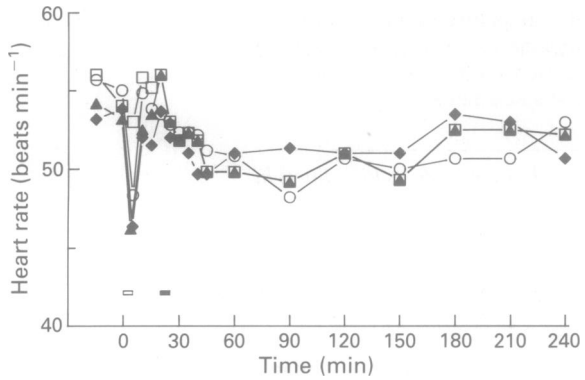

Figure 4 Heart rate after the administration of dexmedetomidine at time 0 min and placebo or three doses of atipamezole between 20 and 25 min. Symbols as in Figure 1, error bars omitted for clarity.

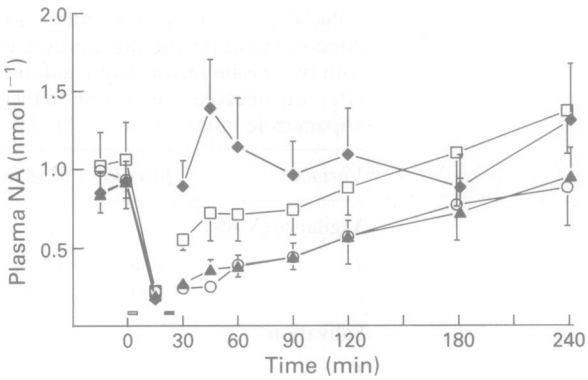

Figure 5 Reduction in plasma noradrenaline concentrations by dexmedetomidine and reversal of this effect by atipamezole. Means ± s.e. mean are presented. Symbols as in Figure 1.

The initial dexmedetomidine-induced blood pressure increase was associated with short-lasting bradycardia (from approx. 55 to 47 beats min^{-1}). Later on, no marked bradycardia was detected during any session and no statistically significant differences could be demonstrated between the treatments, although heart rate was somewhat higher during the high dose atipamezole session than during the other sessions (Table 1, Figure 4).

Plasma noradrenaline

In all sessions, the concentration of NA in plasma was reduced on average by 80% after the administration of dexmedetomidine (Figure 5). After placebo and low dose atipamezole infusions plasma NA concentrations remained low and gradually increased to baseline levels at the end of the sessions. However, 5 min after the lowest atipamezole dose (at 30 min) a slight increase was detected in plasma NA concentrations while in the placebo session the 15 and 30 min values did not differ. Pairwise ANOVA indeed revealed a statistical difference between these two treatments (Tables 1 and 2). The intermediate dose caused a partial reversal of the dexmedetomidine-induced decrease in plasma NA. At 180 min the levels were returned to baseline. The highest dose of atipamezole caused full reversal of plasma NA concentrations, and an overshoot was seen at 45 min. Thereafter, the concentrations of NA remained at or above the basal level throughout the session. All dose levels differed significantly from each other in the period 15–30 min (Tables 1 and 2). During the later part of the sessions plasma NA concentrations were significantly higher after intermediate and high dose treatments ($P = 0.01$ compared with placebo, main effect of dose) than after placebo and low dose treatments (Figure 5).

Discussion

As in previous preclinical studies in laboratory animals and clinical trials in veterinary medicine (Doze *et al.*, 1989; Jalanka, 1989; MacDonald *et al.*, 1989; Savola, 1989; Scheinin *et al.*, 1988; Virtanen, 1989), atipamezole proved to be an effective reversal agent for α_2-adrenoceptor-mediated pharmacological effects. The sedative, sympatholytic, cardiovascular and xerostomic effects of dexmedetomidine, administered 20 min before the reversal agent, were rapidly and entirely counteracted by a 100 times larger dose (on a weight basis) of atipamezole. Only the reversal of bradycardia could not be clearly demonstrated because no marked bradycardia was observed during any session. A dose ratio of 40 : 1 also provided almost full reversal, but with a somewhat slower time course, whereas a 10 : 1 dose only caused partial and minor effects. The rapid awakening of the subjects from dexmedetomidine-induced sleep clearly points to rapid access of atipamezole into the central nervous system also in humans.

After the reversal, no rebound in any effects could be detected in the subjects followed up until four hours. By this time point the effects of dexmedetomidine had subsided also in the placebo session of this study, as in a previous volunteer study with dexmedetomidine (Kallio *et al.*, 1989). The elimination half-life of atipamezole is quite short, 1.5–2 h (Karhuvaara *et al.*, 1990), and it is near the elimination half-life of approximately 2.5 h calculated for dexmedetomidine (Kallio, unpublished results). Both drugs are relatively short-acting as judged from the previous phase I studies (Kallio *et al.*, 1989; Karhuvaara *et al.*, 1990), and the termination of the actions of each drug seems to be related to their elimination and not to redistribution. In this study, a single dose of atipamezole had a sufficiently long duration of action. The reversal of the effects of a longer acting α_2-adrenoceptor agonist, e.g. clonidine, would possibly be followed by rebound effects.

Since large doses of atipamezole are associated with distinct pharmacological effects in human volunteers (Karhuvaara *et al.*, 1989, 1990), the dose of atipamezole used for reversal of α_2-adrenoceptor agonist-induced sedation and other effects should be kept in the lowest effective range. In this study an effective reversal was achieved without any unwanted effects. Single doses of 5 mg have been relatively well tolerated in previous phase I studies, provided that the i.v. injections have been given over several minutes and sufficiently diluted to avoid local irritation (Karhuvaara *et al.*, 1989, 1990). On the basis of the present study, where the dexmedetomidine dose was 50 μg for a 75 kg subject and the administration interval was 20 min, we recommend a

dose ratio range of 40 : 1 to 100 : 1 for atipamezole : dexmedetomidine for use in subsequent clinical studies.

Atipamezole is not active orally (Karhuvaara *et al.*, 1990) and it is therefore not suitable for clinical use when oral dosing is desired. Because of its superior specificity and selectivity (Virtanen *et al.*, 1989) and its rapid access into the central nervous system, it could be an ideal compound for use in clinical situations where rapid reversal of α_2-adrenoceptor agonist effects is wanted. In such cases parenteral administration would anyway be preferable.

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