# Buccal delivery of an $\alpha_2$-adrenergic receptor antagonist, atipamezole, in humans

*Objective:* To evaluate the pharmacokinetics, systemic effects and clinical applicability of buccally administered atipamezole in healthy volunteers.

*Methods:* The study was carried out in two parts. In the first part, spray preparations of atipamezole hydrochloride in water/alcohol (50/50) solution were applied on buccal mucosa of six volunteers. Single doses of 5, 10, 20, and 40 mg atipamezole hydrochloride were administered in ascending order during separate sessions. In the second part, nine subjects received single 20 mg doses as buccal spray, intravenous infusion, or oral solution in randomized order.

*Results:* Values for area under the concentration–time curve for atipamezole (mean ± SD) ranged from 26 ± 4 ng × hr/ml after 5 mg to 112 ± 21 ng × hr/ml after 40 mg and peak concentrations ranged from 11 ± 3 ng/ml after 5 mg to 38 ± 9 ng/ml after 40 mg. Individual peak concentrations were mainly measured at 30 and 60 minutes after administration. Mean elimination half-lives were approximately 1½ hours after every treatment. In part two, a mean bioavailability of 33% was calculated for buccal administration (compared with intravenous), whereas systemic availability after an oral dose was <2%. After intravenous administration the mean total clearance, apparent volume of distribution, and elimination half-life were 1.2 L/hr/kg, 2.9 L/kg, and 1.8 hours, respectively. The intravenous administration of 20 mg atipamezole hydrochloride produced a fivefold elevation in mean plasma norepinephrine concentration, a slight and short-lasting elevation in blood pressure and, in most subjects, increased tension, alertness and restlessness, and sweating. After buccal administration, some subjects reported short-lasting restlessness or tension after the 20 and 40 mg doses. No significant changes in heart rate, blood pressure, or plasma catecholamines were observed. No effects were observed after swallowing of 20 mg atipamezole hydrochloride. The spray caused local reactions at buccal mucosa. Superficial white spots or areas were observed for several hours; these disappeared gradually. Subjects also reported transient numbness at the application site.

*Conclusion:* Atipamezole hydrochloride is well absorbed systemically through oral mucosa. The oral bioavailability of atipamezole is negligible, probably because of extensive first-pass metabolism. (CLIN PHARMACOL THER 1995;58:506-11.)

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Atipamezole is a potent, specific and subtype nonselective $\alpha_2$-adrenergic antagonist.[1] It binds with nearly equal affinity to all three subtypes of $\alpha_2$-adrenergic receptors.[2] Atipamezole increases the release of norepinephrine and antagonizes the sedative, hypotensive, and hypothermic effects of $\alpha_2$-adrenergic receptor agonists in both animals and human subjects.[3-5]

Probably because of an extensive first-pass metabolism, the oral bioavailability of atipamezole is poor[4] and the drug has been given only intravenously thus far. However, if it is to be used in an outpatient setting, alternative modes of administration must be sought. Administration on oral mucosa could be feasible for a drug that may be destroyed in the stomach or intestines or that undergoes extensive first-pass metabolism. Preliminary data from dogs have suggested that atipamezole could be absorbed from oral mucosa. Therefore this study was performed to clarify the clinical applicability, pharmacokinetics, and systemic effects of buccally administered atipamezole in healthy volunteers.

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## METHODS

***Subjects.*** The study was performed in healthy male volunteers. Each subject gave written informed consent. The study protocol was approved by the Joint Ethics Committee of Turku University and Turku University Central Hospital. The subjects ranged in age from 19 to 26 years; weight range was from 62 to 84 kg and height range was from 171 to 192 cm.

***Design.*** The study consisted of two parts. First, an open-label dose-escalating phase with buccal atipamezole was performed in six subjects to see if measurable drug concentrations in serum could be achieved. In the second part, a fixed dose determined after the first part was given in a randomized (Latin square) order buccally, orally, and intravenously to nine subjects. During the second part, one person was withdrawn from the study because of adverse effects and was replaced by another volunteer. At least 3 days elapsed between drug administrations to a given volunteer.

***Drug administration.*** In the first part of the study, each subject received buccally single atipamezole hydrochloride doses of 5, 10, 20, and 40 mg in ascending order. In the second part, the dose was 20 mg. For buccal administration, atipamezole hydrochloride was dissolved in 50% ethanol. The drug solutions contained either 50 mg/ml (5 mg dose) or 100 mg/ml (other dose levels) atipamezole hydrochloride. One to four shots were given from the bottles equipped with an atomizer designed to deliver 100 μl at each push. To calculate the actual drug amount given, the bottles were weighed before and after drug administration. The actual doses were used in the pharmacokinetic calculations. For intravenous use, injectable atipamezole was diluted with physiologic saline solution to give a final concentration of 1 mg/ml. This solution was infused at a rate of 2 ml/min for 10 minutes with use of an infuser (Perfusor ED 2, B. Braun, Melsungen, Germany). For oral administration, subjects received injectable atipamezole that was diluted with tap water to a final volume of 100 ml. The drugs were manufactured and delivered by Orion Corporation, Orion-Farmos, Turku, Finland.

***Assessments.*** Venous blood samples (10 ml) for the determination of atipamezole were drawn before drug administration and ¼, ½, 1, 1½, 2, 3, 4, and 6 hours thereafter. During the second part of the study, additional samples were collected at ¾ and 5 hours. Atipamezole concentrations in serum were determined with gas chromatography-mass spectrometry with use of a modification of the analytic method originally developed for medetomidine.[6] The quantification limit of the assay was 0.05 ng/ml. Interassay coefficient of variation ranged from 6.9% at 0.5 ng/ml to 4.5% at 80 ng/ml. Pharmacokinetic calculations were performed with Biopak and PCNONLIN programs (SCI Software, Lexington, Ky.) in parts one and two, respectively. The calculated pharmacokinetic parameters included peak concentration ($C_{max}$), time to peak $C_{max}$ ($t_{max}$), half-life of the absorption phase ($t_{½a}$), area under the concentration–time curve (AUC), bioavailability, elimination half-life ($t_{½}$), total clearance (CL), and apparent volume of distribution at steady state ($V_{SS}$).

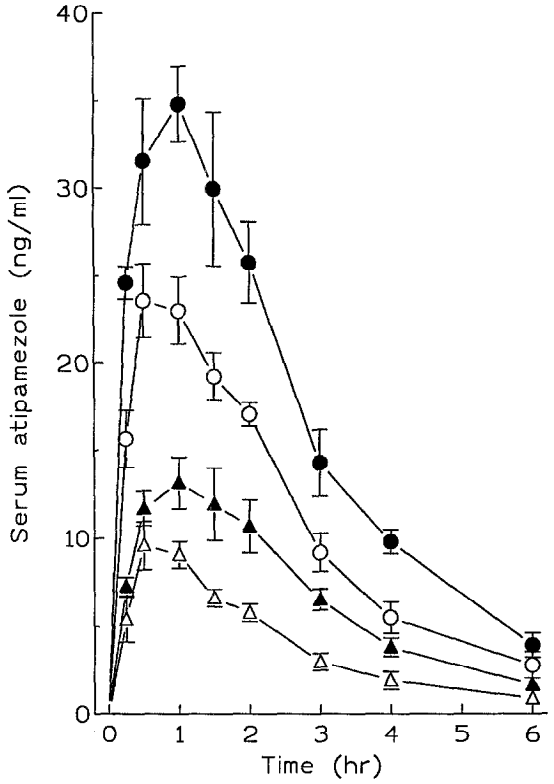


**Fig. 1.** Mean (SE) serum atipamezole concentrations in six subjects after buccal doses of 5 mg *(open triangles)*, 10 mg *(solid triangles)*, 20 mg *(open circles)*, and 40 mg *(solid circles)*.

Samples for plasma norepinephrine and epinephrine concentration determinations were drawn before drug administration and ½, 1, and 2 hours thereafter. The samples were placed in an ice bath and processed promptly in a refrigerated centrifuge. Determinations were performed with HPLC with coulometric detection.[7]

Blood pressure and heart rate were determined with an automated sphygmomanometer BP-203 (Nippon Colin, Tokyo, Japan), always immediately after the

**Table I.** Pharmacokinetic parameters of atipamezole after buccal administration of 5, 10, 20, and 40 mg

| *Parameter* | *5 mg* | *10 mg* | *20 mg* | *40 mg* | *ANOVA** | |
|---|---|---|---|---|---|---|
| | | | | | $F_{3,15}$ | *p Value* |
| AUC (ng × hr/ml) | 26 ± 4 | 44 ± 10 | 74 ± 13 | 112 ± 21 | 98.3 | <0.0001 |
| $C_{max}$(ng/ml) | 11 ± 3 | 15 ± 4 | 26 ± 4 | 38 ± 9 | 45.3 | <0.0001 |
| $t_{max}$(hr) | 0.6 ± 0.3 | 0.8 ± 0.4 | 0.8 ± 0.4 | 0.8 ± 0.3 | 1.35 | 0.71 |
| $t_{1/2}$(hr) | 1.5 ± 0.4 | 1.5 ± 0.3 | 1.6 ± 0.5 | 1.6 ± 0.4 | 0.06 | 0.89 |

Data are mean values ± SD ($n$ = 6).
AUC, Area under the concentration–time curve; $C_{max}$, peak concentration; $t_{max}$, time reach $C_{max}$; $t_{1/2}$, elimination half-life.
*ANOVA for log-transformed data, except Friedmans nonparametric ANOVA for $t_{max}$. ANOVA for AUC/dose: $F$ = 11.9, $p$ = 0.0003; for $C_{max}$/dose: $F$ = 22.0, $p < 0.0001$.

**Table II.** Pharmacokinetic parameters of atipamezole after intravenous, buccal, and oral administration

| *Parameter* | *Intravenous* | *Buccal* | *Oral* |
|---|---|---|---|
| Actual dose (mg) | 20 | 22.8 ± 0.5 | 20 |
| AUC (ng × hr/ml) | 231 ± 40 | 85 ± 16 | 4.2 ± 0.6 |
| $F$ (%) | — | 32.5 ± 6.1 | 1.9 ± 0.3 |
| $C_{max}$(ng/ml) | 145 ± 81 | 23.0 ± 3.9 | 1.2 ± 0.3 |
| $t_{max}$(hr) | — | 0.76 ± 0.25 | 0.82 ± 0.39 |
| $t_{1/2a}$(hr) | — | 0.41 ± 0.62 | 0.26 ± 0.19 |
| $t_{1/2}$(hr) | 1.8 ± 0.2 | 2.0 ± 0.4 | 2.0 ± 0.3 |
| CL (L/hr/kg) | 1.2 ± 0.2 | — | — |
| $V_{SS}$(L/kg) | 2.9 ± 0.7 | — | — |

Data are mean values ± SD ($n$ = 9).
$F$, Bioavailability; $t_{1/2a}$, half-life of the absorption phase; CL, total clearance; $V_{SS}$, apparent volume of distribution at steady state.

blood samples had been drawn. The subjects were supine during the first 2 hours and were then allowed to move about the laboratory. However, bed rest was always initiated 10 minutes before blood sampling and other readings.

The subjective degree of vigilance and tension were evaluated repeatedly with a 100 mm visual analog scale (VAS) and the subjects were urged to report any subjective effects.

***Statistical analysis.*** ANOVA and ANOVA for repeated measures designs were used in the statistical evaluation. Calculations were performed with BMDP software (Statistical Software Inc., Los Angeles, Calif.) and SAS software (SAS Institute, Cary, N.C.). A $p$ value less than 0.05 was considered to be statistically significant. When pairwise comparisons were made as post hoc tests, Bonferroni-corrected $p$ values were used. The analysis of hemodynamic parameters was performed separately for the first 2 hours (the time the subjects were supine) and for the remainder of the time.

## RESULTS

***Part 1.*** Atipamezole was absorbed from the buccal mucosa, but the relative amount absorbed diminished with increasing dose (Fig. 1 and Table I). The $t_{max}$ in serum and $t_{1/2}$ of the terminal elimination phase were about ¾ and 1½ hours, respectively, with no difference between the doses.

None of the buccal atipamezole doses affected plasma epinephrine or norepinephrine concentrations, blood pressure, or heart rate; small elevations in the heart rate were seen after 2 hours when the subjects were allowed to stand, but the effects were similar after all dose levels and presumably due to upright posture.

Some subjects had mild to moderate subjective systemic effects after the highest doses: relaxation and restlessness were each reported by one person after 20 mg buccal atipamezole, and four subjects had these symptoms or headache after the highest dose. No systematic shifts in VAS scores for vigilance and tension occurred.

Superficial white spots or white areas were ob-

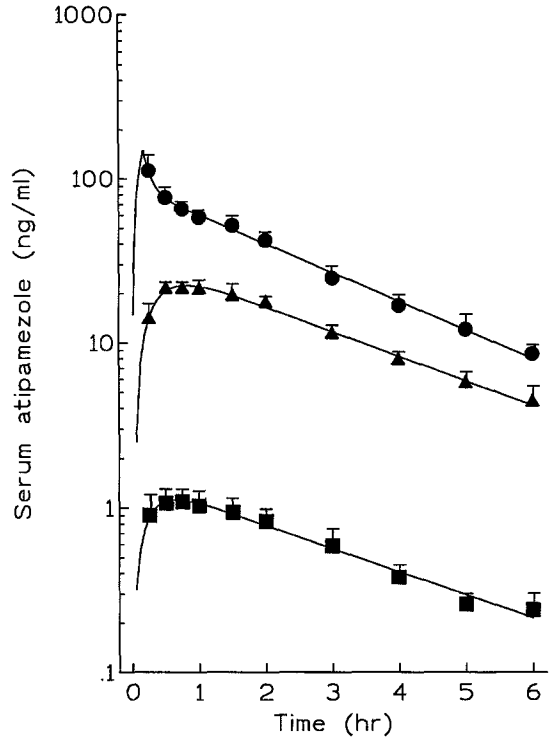


**Fig. 2.** Mean (SE) serum atipamezole concentrations in nine subjects after 20 mg given intravenously *(circles)*, buccally *(triangles)*, or orally *(squares)*.

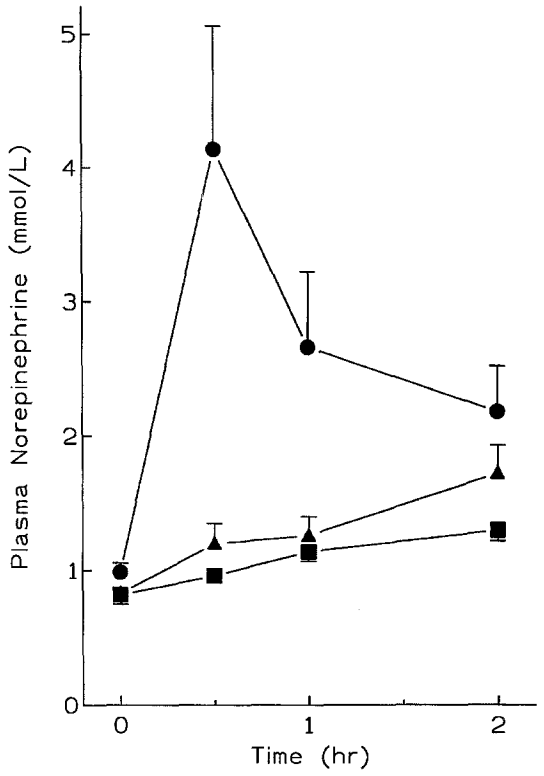


**Fig. 3.** Mean (SE) plasma norepinephrine concentrations in nine subjects after 20 mg given intravenously *(circles)*, buccally *(triangles)*, or orally *(squares)*.

served regularly after application of the spray that contained 100 mg/ml atipamezole, whereas use of the 50 mg/ml spray did not produce such effects. The appearance of mucosa gradually returned to normal within a few hours, and no permanent changes were observed. Some subjects reported transient numbness at the application site.

***Part 2.*** The main pharmacokinetic parameters of atipamezole after intravenous, buccal, and oral administration are summarized in Table II and the corresponding concentration–time curves are shown in Fig. 2. After an intravenous infusion, atipamezole was eliminated from the body, with a mean elimination phase $t_{1/2}$ and CL of 1.8 hours and 1.2 L/hr/kg, respectively. The $V_{SS}$ (about 217 L or 2.9 L/kg) was high. The bioavailability of buccal atipamezole was about 33%, whereas only negligible amounts (<2%) of the drug were found systemically after oral administration. The mean $t_{1/2a}$ was 0.4 hour after buccal administration, but the interindividual variation was high (Table II).

A fivefold increase in plasma norepinephrine was evident after intravenous atipamezole, whereas practically no changes occurred after oral or buccal administration of the 20 mg dose (Fig. 3). Both systolic and diastolic blood pressures were elevated by 7 to 8 mm Hg during the first 2 hours after intravenous atipamezole. Pairwise statistical comparisons (systolic blood pressure) resulted in $p$ values of 0.02 (intravenous versus oral, treatment × time interaction) and 0.04 (intravenous versus buccal, main effect of treatment).

VAS scores for vigilance and tension were increased only after intravenous atipamezole. In line with this, all subjects had subjective effects after administration of intravenous atipamezole. They reported sweating, salivation, cold shivering, tremor, or feelings of increased tension. The effects usually started at the end of the 10-minute infusion or shortly thereafter and resolved rapidly. In one subject the infusion was stopped prematurely after 3 minutes (corresponding to a dose of about 6 mg atipamezole) because of a feeling of compression in the forehead and pressure behind the eyes; this subject also reported headache and

narrowing of vision. After cessation of the infusion, the symptoms disappeared within 10 minutes, with the exception of headache, which persisted for 1 to 2 hours. Increased tension, tremor, or feelings of warmth were reported after administration of buccal atipamezole. As in part 1, white spots were observed on buccal mucosa after atipamezole spray. Atipamezole given orally caused no subjective effects.

## DISCUSSION

This study shows that atipamezole is absorbed from buccal mucosa to circulation, with a bioavailability of about 33%. Furthermore, the absorption from oral mucosa is reasonably uniform. The coefficients of variation both in fraction absorbed and in buccal AUC are below 20% and closely resemble the variation of AUC recorded after intravenous atipamezole (Table II).

AUC and $C_{max}$ values increased with dose but in a nonproportional manner; the values differed significantly still after correction for dose (Table I). Other pharmacokinetic parameters were similar over the dose range studied. Values for CL and volume of distribution for atipamezole recorded here were similar to those reported earlier after 10 to 100 mg intravenous doses of atipamezole.[4] In an earlier study, atipamezole concentrations in plasma after oral dosing were undetectable and its bioavailability was considered to be very poor[4]; this conclusion was corroborated in the present study in which a more sensitive method of determination was used. The reason for the negligible oral bioavailability of atipamezole is currently unknown, but it may reflect an extensive first-pass metabolism.

The subjective effects that some of the volunteers had (restlessness, increased tension, and sweating) were mild to moderate and easily explainable by the pharmacologic effects of $\alpha_2$-antagonists.[8-11] Four subjects reported restlessness or headache after buccal administration of 40 mg atipamezole. Relaxation of the legs and restlessness of the legs were each reported by one person after 20 mg in part 1 of the study, whereas no subjective symptoms occurred at lower doses. In part 2 of the study, one subject had tremor after buccal administration of 20 mg atipamezole, an effect usually associated with the intravenous administration only, Several others complained of increased tension of a mild to moderate degree. This suggests that 20 mg atipamezole as a spray lies at the over limit of tolerability of its buccal use; many subjects had subjectively unpleasant adverse effects at that dose level, although the intensity of the adverse effects was only mild to moderate.

In this study, plasma epinephrine, norepinephrine, and heart rate were practically unchanged after buccal administration of atipamezole. On the other hand, administration of intravenous atipamezole was associated with clear, subjectively unpleasant adverse effects and elevation of plasma norepinephrine. This may be because of the high concentration of atipamezole in serum after intravenous administration (mean venous $C_{max}$ values were 145 ng/ml and 23 ng/ml after 20 mg atipamezole given intravenously and buccally, respectively) or to the rapid increase of atipamezole concentration during the infusion. After intravenous administration the subjective effects usually disappeared after 1 hour, when the drug concentration had decreased to values around 60 ng/ml.

$\alpha_2$-Antagonists such as atipamezole have the potential to be used for several diseases. The oral bioavailability of atipamezole is negligible, and only the parenteral mode of administration has been used thus far in humans. We have now shown in humans that atipamezole is absorbed from oral mucosa and that the bioavailability is high and uniform enough to be used clinically.

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