Cognitive effects of β-adrenergic antagonists after single doses: Pharmacokinetics and pharmacodynamics of propranolol, atenolol, lorazepam, and placebo

The behavioral effects of two β-adrenergic receptor antagonists, selected to represent differing lipophilicity, were evaluated in a double-blind, single-dose, parallel-group study. A group of 55 healthy volunteers (mean age, 28 years) received single oral doses of placebo, atenolol (50 mg), propranolol (40 mg), or lorazepam (2 mg). Plasma drug concentrations, self-ratings of sedation and mood, observer ratings of sedation, and performance on the Digit Symbol Substitution Test (DSST) were assessed at multiple times during 24 hours after drug administration. Information acquisition and recall were tested at 3 and 24 hours after drug administration. Lorazepam significantly increased sedation and fatigue, impaired DSST performance, and impaired memory. The time course of these changes was highly consistent with plasma lorazepam concentrations. In contrast, atenolol and propranolol produced at most small changes in self-ratings and observer ratings and did not alter DSST performance or memory. Under experimental conditions that are sensitive to the depressant effects of a typical benzodiazepine, single doses of atenolol and propranolol produced no meaningful changes, compared with placebo. (CLIN PHARMACOL THER 1993;53:577-84.)

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β-Adrenergic receptor antagonists are used widely for the treatment of cardiovascular disease. All drugs of this class have the fundamental property of producing peripheral β-adrenergic antagonism. However, there are differences among the various agents in their pharmacokinetic properties[1-3] and in their secondary pharmacologic effects, such as "membrane-stabilizing" properties, intrinsic sympathomimetic activity, and cardioselectivity.[4] The various β-blockers also differ in lipophilicity.[5,6] Theoretically, the equilibrium brain:free plasma concentration ratio for a β-blocker should increase in proportion to its lipid solubility. This relationship has been confirmed in some studies.[7-12] It has also been suggested that a high degree of brain uptake of relatively lipophilic β-antagonists may contribute to central nervous system (CNS) side effects of these drugs (such as lethargy, fatigue, nightmares, and possibly depression) reported during long-term dosing.[13] As such, β-antagonists with relatively low lipid solubility may produce a lower incidence of CNS side effects.[13-17] However, the clinical validity of this hypothesis has not been clearly established.[18,19]

This study used the single-dose paradigm to evaluate the systemic pharmacokinetics and the effects on mood, psychomotor performance, and memory of the most lipophilic β-antagonist, propranolol, in comparison with a relatively nonlipophilic β-antagonist, atenolol. Both of these drugs were evaluated in comparison to placebo and to lorazepam, a "positive" control. Lorazepam is a widely used benzodiazepine de-

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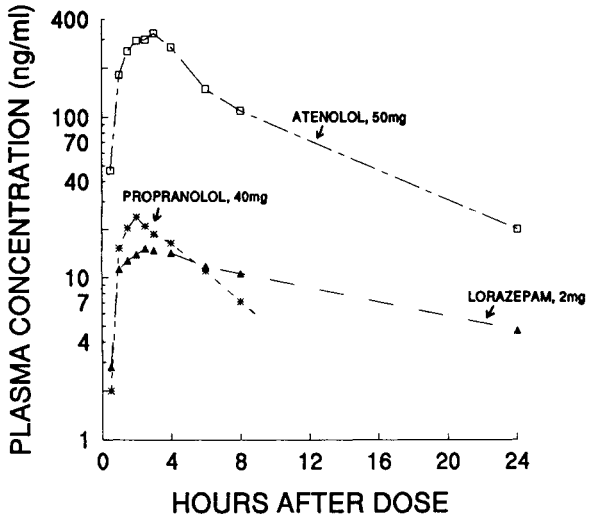

Fig. 1. Plasma concentrations of atenolol, propranolol, and lorazepam. Each *point* is the mean value for all subjects at the corresponding time. See Table I for pharmacokinetic analysis.

rivative known to produce sedative and performance-impairing effects after single doses.[20]

METHODS

Subjects. A total of 55 healthy young volunteers (24 women and 31 men), aged 20 to 44 years (mean age, 28 years) participated in the study. Each subject gave written informed consent. All were healthy, active, ambulatory adults; none had a history of medical disease, and none were receiving other medications. Female subjects did not use oral contraceptive steroids. Twenty-two of the subjects were cigarette smokers; the remainder were nonsmokers.

Procedure. Subjects participated in a single dose, double-blind, parallel-treatment study. They were randomly assigned to one of the following four treatment conditions: (1) placebo, (2) 50 mg atenolol, (3) 40 mg propranolol, or (4) 2 mg lorazepam. All medications were packaged identically.

Subjects fasted overnight before drug administration, and ingested a light liquid breakfast 2 to 3 hours before dosage. They continued to fast until 3 hours after dosing, when they resumed a normal diet.

A single oral dose of the appropriate medication was given at approximately 9 AM with 100 to 200 ml tap water. Venous blood samples were drawn from an indwelling canula into heparinized tubes before dosing and at the following times after administration: ½, 1, 1½, 2, 2½, 3, 4, 6, 8, and 24 hours. Blood samples were centrifuged, and the plasma was separated and frozen until the time of assay.

Sedative effects and mood state were rated on 100 mm visual analog scales[21-26] by the subjects themselves and by a trained observer who was unaware of the treatment condition. Ratings were obtained twice before medication administration and at ½, 1, 2, 3, 4, 6, 8, and 24 hours after dosing. The digit symbol substitution test[21-26] (DSST) also was administered twice before dosing and at the times described above. Subjects were asked to make as many correct symbol-for-digit substitutions as possible within 2 minutes. For each DSST, the subjects completed one of 100 randomly selected variants of the test, so that no individual took the same test more than once.

Information acquisition and recall were evaluated by use of a word-list test procedure.[21-26] At 3 hours after medication administration, a list of 16 words, taken from four different categories, was read in random order. Recall was tested after each of six consecutive presentations of the list, each time with the words in a different random order. Twenty-four hours after dosing, subjects were first asked to recall as many words as possible from the previous day's list (free recall). The learning procedure was then repeated, with the same list presented in six different random sequences.

Analysis. Plasma concentrations of lorazepam were determined by gas chromatography with electron capture detection.[27,28] Propranolol and atenolol plasma levels were measured by high performance liquid chromatography.[29,30] Peak plasma concentration and the time of peak concentration were used to estimate the rate of drug appearance in the systemic circulation. The slope (β) of the terminal log-linear phase of the plasma concentration curve was determined by linear regression analysis and used to calculate the apparent elimination half-life. The area under the plasma concentration curve (AUC) up to the final detectable concentration was measured by use of the linear trapezoidal method and extrapolated to infinity. Oral clearance was calculated as the administered dose divided by total AUC.

For each of the visual analog scales, the two ratings obtained before dosing were averaged (the baseline value), and all subsequent scores were expressed as the increment or decrement relative to this average predose value. Scores on the DSST were similarly analyzed, except that only the second of the predose trials was used as the baseline. This was done to accommodate the practice effects on performance testing.

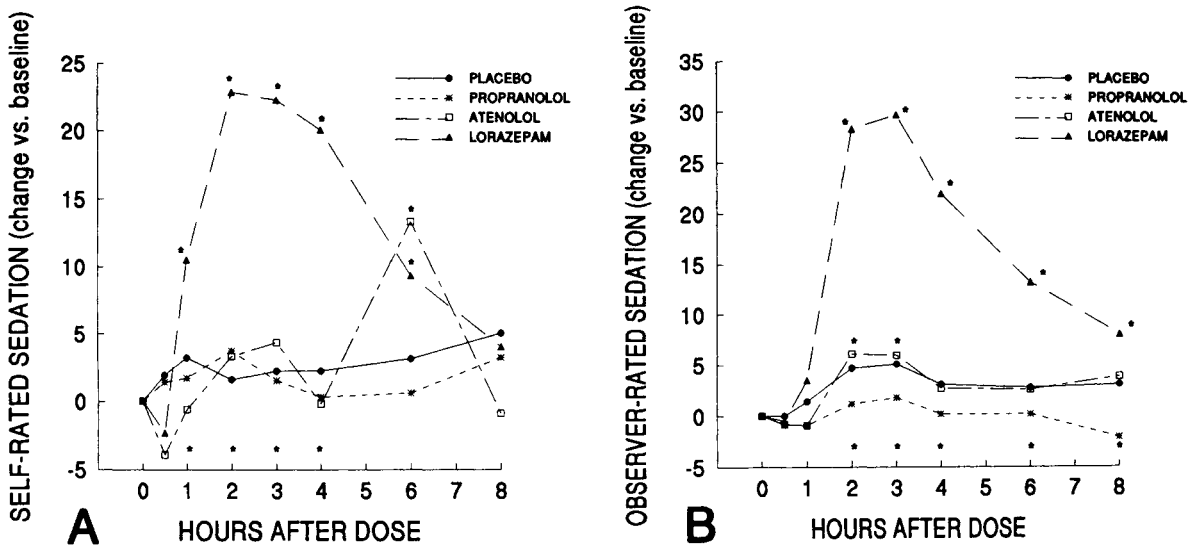

Fig. 2. Changes over predose baseline in self-rated sedation **(A)** and observer-rated sedation **(B)** in the four treatment conditions. Each *point* is the mean value for all subjects at the corresponding time. *Asterisk* (*) along the x-axis indicates significant ($p < 0.05$) differences among the four treatment condition based on ANOVA. *Asterisk* (*) above individual data points indicates a significant ($p < 0.05$) difference from zero change.

Table I. Summary of pharmacokinetic variables

	Propranolol	*Atenolol*	*Lorazepam*
Peak plasma concentration (ng/ml)	24.9 ± 5.4	372 ± 48	16.2 ± 1.0
Time of peak (hr after dose)	2.1 ± 0.3	2.3 ± 0.2	2.1 ± 0.2
Elimination $t_{1/2}$ (hr)	3.4 ± 0.3	6.4 ± 0.3	13.8 ± 1.1
Total AUC (ng/ml · hr)	151 ± 38	2812 ± 242	319 ± 31
Oral CL (ml/min)	6623 ± 1086	321 ± 23	120 ± 14

Data are mean values ± SEM.
$t_{1/2}$, Half-life; AUC, area under the plasma concentration curve; CL, clearance.

Results of the word-list memory test were analyzed as absolute scores.

Statistical procedures included linear regression, ANOVA, Student *t* test, and the Fisher exact test.

RESULTS

The four treatment groups did not differ significantly in subjects' mean age or body weight, in the distribution of men versus women, or in the distribution of smokers versus nonsmokers.

Fig. 1 and Table I show mean plasma concentrations and pharmacokinetic variables for the three groups receiving active medications. Mean values of t_{max} occurred between 2 and 3 hours after dosing in all treatment groups. Pharmacokinetic variables for propranolol, atenolol, and lorazepam are consistent with previous reports.[1-3,31,32]

Among subjects receiving lorazepam, significant increases over baseline occurred in self-ratings and observer ratings of sedation (Fig. 2), and the ratings were significantly intercorrelated (Fig. 3). There were similar increases in self-ratings of fatigue and feeling "spacey" (Fig. 4). Changes were initially observed at 1 to 2 hours after dosing and persisted for up to 6 hours after dosing.

The relation of plasma lorazepam concentration to rating scale changes indicated no evidence of clockwise or counterclockwise hysteresis (Fig. 5). The plasma level versus response relationships were consistent with a function of the form: $y = Bx^A$.

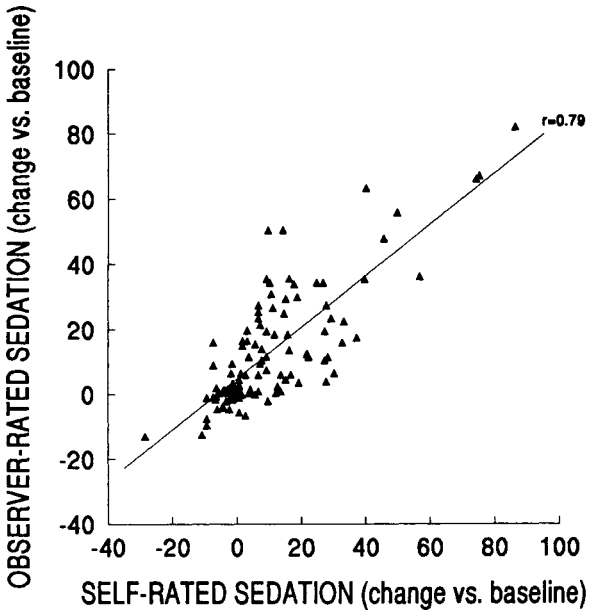

Fig. 3. Relation between changes over baseline in self-ratings of sedation (x-axis) and in observer ratings of sedation (y-axis) among recipients of lorazepam. Each time point for each individual subject is shown. *Solid line* was determined by linear regression analysis ($r = 0.79$, $p < 0.001$).

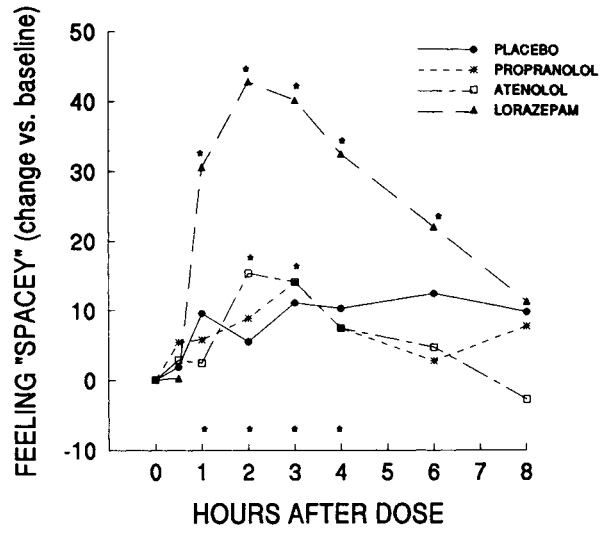

Fig. 4. Changes over predose baseline in self-ratings of feeling "spacey" in the four treatment conditions. Each *point* is the mean value for all subjects at the corresponding time. *Asterisks* (*) have the same meanings as in Fig. 2.

In contrast to lorazepam, few significant differences from baseline were observed in the propranolol, atenolol, and placebo treatment groups. Exceptions were, in the atenolol group, an increase in self-rated sedation at 6 hours after dosing and small but significant increases in observer-rated sedation and in self-ratings of feeling spacey at 2 and 3 hours after dosing (Figs. 2 and 4). In the propranolol group, self-ratings of fatigue were slightly but significantly increased over baseline at 2 hours after dosing.

In the propranolol, atenolol, and placebo treatment groups, DSST scores improved over time relative to the baseline, consistent with practice or learning effects (Fig. 6). However, in the lorazepam group, DSST scores were reduced relative to baseline, and relative to the other conditions, between 2 and 6 hours after dosing (Fig. 6). In subjects receiving lorazepam, self-rated and observer-rated sedation scores were significantly correlated with changes in DSST scores (Fig. 7).

The number of words recalled averaged 13.5 of 16 among the subjects who received placebo (Table II). This was slightly reduced, to 12.4 and 11.5 words, respectively, in the atenolol and propranolol groups. Among subjects in the lorazepam group, an average of 10.6 words was learned. The difference among the four groups just failed to reach significance at the 0.05 level based on ANOVA ($F = 2.69$; $p < 0.06$). Dunnett's test indicated that the lorazepam-placebo difference was significant ($p = 0.05$), whereas differences between placebo and atenolol or propranolol conditions were not significant. When free recall was tested at 24 hours after dosing, differences among groups were highly significant ($F = 13.95$, $p < 0.0001$). A mean of 12.9 words was recalled by placebo recipients; this was slightly and not significantly reduced to 11.9 and 11.7 words in the atenolol and propranolol groups, respectively. However, among recipients of lorazepam, an average of only 6.2 words were recalled at 24 hours after dosing. After the 6 relearning trials at 24 hours, differences among the four treatment conditions were not significant.

DISCUSSION

Adverse CNS effects of β-adrenergic antagonists are generally of concern during long-term treatment of hypertension or heart disease. Nonetheless, the single-dose study paradigm has proved to be extremely useful in evaluating the time course and intensity of CNS effects of many centrally acting compounds, the relation of these changes to plasma drug concentrations, and differences among drugs both within class and between class. This study evaluated the pharmacokinet-

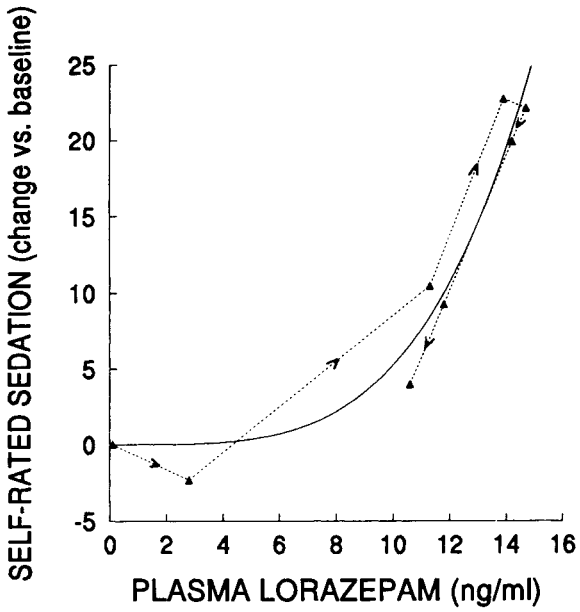

Fig. 5. Relation of mean plasma lorazepam concentrations (x-axis) to mean change over baseline in self-rated sedation (y-axis). Actual data points *(solid triangles)* are connected by *broken lines*, with *arrows* indicating the direction of increasing time. *Solid line* represents the function of best fit consistent with the equation $y = Bx^A$ ($B = 6.3 \times 10^{-4}$; $A = 3.92$).

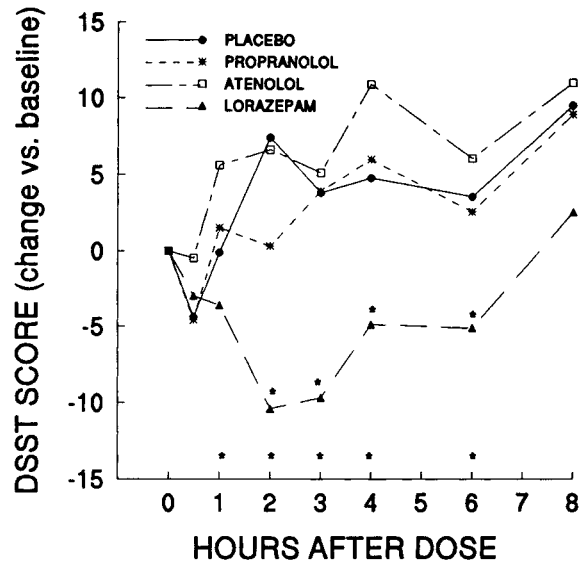

Fig. 6. Changes over predose baseline in scores on the Digit Symbol Substitution Test (DSST). Each *point* is the mean value for all subjects at the corresponding time. *Asterisk* (*) along the x-axis indicates significant ($p < 0.05$) differences among the four treatment conditions based on ANOVA. *Asterisk* (*) above individual data points indicates significant ($p < 0.05$) difference from the value in the placebo group at that time based on Dunnett's t test.

ics and pharmacodynamic effects of clinically comparable single doses of two β-antagonists, propranolol and atenolol, in healthy young volunteers. The effects of these two medications were compared with placebo and with a high therapeutic dose of the benzodiazepine derivative lorazepam. The tests of mood, psychomotor performance, and memory used in this study have been extensively used in previous studies from our laboratory[22-26] and elsewhere.[33-39] These tests are well established to be sensitive to the CNS depressant effects of drugs such as alcohol, barbiturates, and the benzodiazepine derivatives.

The effects of lorazepam are very similar to those observed in previous studies of this drug.[25,26,38,40-43] Lorazepam significantly increased self-rated and observer-rated sedation, with a high correlation between self-ratings and observer ratings. Lorazepam also produced significant increases in self-rated fatigue and in the sensation of feeling spacey. The time course of these changes was consistent with the time course of plasma lorazepam concentrations. Effects were maximal at 2 to 3 hours after dosing, approximately corresponding to the time of maximum plasma levels. As

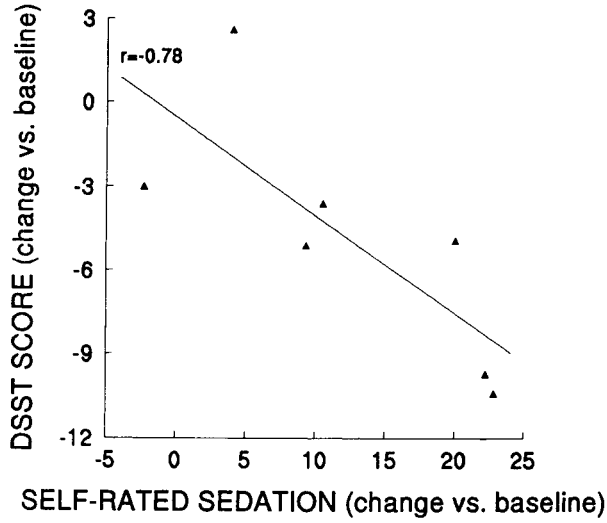

Fig. 7. Mean values of self-rated sedation (x-axis) versus mean changes in DSST score (y-axis) among subjects in the lorazepam treatment group. Each *point* is the mean value for all subjects at the corresponding time. *Solid line* was determined by linear regression analysis ($r = -0.78$, $p < 0.05$).

Table II. Drug effects on information acquisition and recall

	Mean ± SEM words recalled (of 16)		
	Six initial learning trials (at 3 hr)	*Free recall (at 24 hr)*	*Six relearning trials (at 24 hr)*
Treatment condition			
Placebo	13.5 ± 0.6	12.9 ± 0.7	14.1 ± 0.7
Atenolol	12.4 ± 0.8	11.9 ± 0.9	13.8 ± 0.6
Propranolol	11.5 ± 1.0	11.7 ± 0.9	13.7 ± 0.8
Lorazepam	10.6 ± 0.6*	6.2 ± 0.7*	13.7 ± 0.5
Result of ANOVA among four treatments	$F = 2.69$; $p < 0.06$	$F = 13.95$; $p < 0.0001$	$F = 0.10$; NS

*Significant difference from placebo value based on Dunnett's test.
NS, Not significant.

reported in a previous study of diazepam,[44] the concentration-response relationship was consistent with an equation of the form $y = Bx^A$. This can be seen as a modification of a sigmoid E_{max} relationship, for which a maximum effect has not been attained and a 50% effective concentration (EC_{50}) cannot be determined. The lack of evident clockwise hysteresis in the concentration-response profile suggests that acute tolerance to lorazepam is not evident under conditions of this study.[40,41]

Lorazepam also significantly impaired performance on the DSST, a psychomotor performance test used widely to evaluate the time course and intensity of pharmacodynamic effects of benzodiazepines and other drugs with CNS-depressant properties.[21-26,37-39] As with the rating scale changes, DSST alterations attributable to lorazepam were consistent with plasma lorazepam concentrations and were also significantly correlated with self-ratings and observer ratings of sedation.

Lorazepam significantly impaired the capacity for immediate recall of a list of 16 words presented at 3 hours after dosing, close to the time of both maximum plasma lorazepam concentrations and maximum effects on the other pharmacodynamic tests. At 24 hours after dosing there was a large and highly significant "loss" of the information that was acquired. Again, these findings are consistent with the dose- and concentration-dependent impairment of information acquisition and of subsequent storage and delayed recall produced by lorazepam[25,26,42] and by all other benzodiazepine derivatives.[22,24,38,45-47] "Relearning" of a 16-word list at 24 hours after dosing was unimpaired, indicating that the amnesic effect is transient and reversible.

The doses of propranolol and atenolol used in this study are in the low range of single doses used clinically. These doses, or lower doses, have been administered to treat anxiety or panic disorder.[48,49] Although we did not objectively verify the production of peripheral β-antagonism in this study, many previous reports indicate that significant peripheral β-antagonism is caused by these doses and plasma concentrations of propranolol and atenolol.[50-56] In contrast to lorazepam, the two β-antagonists produced minimal if any changes in the same tests of mood, psychomotor performance, and memory. These two drugs represent opposite ends of the scale of β-blocker lipid solubility,[5,6] a property that has been implicated in a potentially different incidence of CNS side effects during multiple-dose therapeutic use.[13] The findings from the present single-dose study confirm other reports that used both single-dose and multiple-dose design,[18,57-63] indicating that differing lipid solubility of β-antagonists has, at most, a small influence on the occurrence of adverse CNS effects.

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