Effects of procainamide on intra-arterial electrograms during atrial fibrillation: implication for detection algorithms

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ABSTRACT The effects of antiarrhythmic drugs on electrograms have implications for arrhythmia-detection algorithms in implantable antitachycardia devices. Filtered and unfiltered intra-atrial electrograms were analyzed in eight patients who received procainamide (50 mg/min iv, up to 1000 mg) during 11 episodes of atrial fibrillation. Continuous recordings were made before, during, and after the infusion. The recordings were digitized, divided into 4.27 sec segments, and analyzed for atrial rate, median frequency and amplitude probability density function. Significant differences were noted before and after infusion of procainamide for atrial rate (498 ± 97 vs 356 ± 146 beats/min; p < .005), median frequency (5.50 ± 1.22 vs 4.24 ± 0.99 Hz; p < .0005), and density (58.3 ± 13.9% vs 69.1 ± 15.0%; p < .005). Pre- and postprocainamide values were compared with published criteria for detection of atrial fibrillation. Before procainamide, only 2.3%, 5.7%, and 3.4% of the data segments failed to meet criteria for atrial fibrillation by rate, frequency content, and density, respectively. In contrast, after procainamide, 50%, 36.4%, and 28.4% of the data segments failed to meet these same criteria, despite electrograms still meeting morphologic criteria for atrial fibrillation. Thus procainamide resulted in changes sufficient to cause failure of published criteria for detection of atrial fibrillation. These findings have broad implications for the function of antitachycardia devices in patients receiving antiarrhythmic drug therapy.


WHEN COMPUTER algorithms are designed to detect arrhythmias, an assumption is made that the signal characteristics of the arrhythmia are constant under variable clinical conditions. However, a number of clinical variables may alter these signal characteristics, such as changes in ventricular electrogram characteristics in relation to the time after onset of ventricular fibrillation, changes in atrial electrogram amplitude during exercise, and changes in electrogram amplitude and rate caused by lead maturation. We hypothesized that antiarrhythmic drugs might also change electrogram characteristics. If such changes were to occur, algorithms would have to be robust enough to accommodate these changes and still provide adequate detection. We chose to examine the effects of one antiarrhythmic drug, procainamide, on intra-atrial electrogram characteristics during atrial fibrillation. Recently, our laboratory has reported success with an algorithm that utilizes rate, amplitude probability density, and power spectrum measurements to differentiate atrial electrograms during atrial fibrillation and regular tachycardias. In the present study we examined changes in these electrogram characteristics during intravenous infusion of procainamide. To our knowledge, this is the first formal study of the effects of a changing antiarrhythmic drug milieu on the reliability of arrhythmia detection algorithms.

Methods

Patients Eight consecutive patients who received an intravenous infusion of procainamide during atrial fibrillation in the electrophysiology laboratory comprised the study population. The patients' ages ranged from 19 to 73 years (mean 42). One patient was studied on two occasions separated by 4 months and one patient received three separate infusions of procainamide during three episodes of atrial fibrillation in one study. Thus there was a total of 11 infusions available for analysis. Indications for electrophysiologic testing included Wolff-Parkinson-White syndrome complicated by paroxysmal atrial fibrillation.
(four patients), ventricular tachycardia complicating coronary artery disease (three patients), and palpitations with near syncope in one patient with hypertrophic cardiomyopathy. Two of the patients with coronary disease had chronic atrial fibrillation, while the other six patients had atrial fibrillation induced in the laboratory either directly (four patients) or via spontaneous degeneration during atrioventricular reentrant tachycardia (two patients). The two patients with coronary artery disease and chronic atrial fibrillation were taking digoxin for heart failure and control of the ventricular response to atrial fibrillation. The remaining six patients were studied in the absence of cardioactive medications.

**Recordings.** Recordings were made in the course of routine electrophysiologic testing. In each case, a No. 7F quadrupolar catheter (USCI, Billerica, MA) was introduced percutaneously via a femoral vein and positioned in the right atrium with the tip at the junction with the superior vena cava. Interelectrode spacing was 1 cm. Bipolar high right atrial electrograms as well as surface leads were amplified by a physiologic recorder (Honeywell VR-16; Electronics for Medicine, Honeywell Inc., Pleasantville, NY). Both filtered (30 to 500 Hz) and unfiltered (0.05 to 5000 Hz) intra-atrial data were continuously recorded before, during, and after infusion of procainamide and stored on FM tape (Honeywell 101; Electronics for Medicine). Although all data were filtered in some manner during data processing, the terms “filtered” and “unfiltered” will be used hereafter to differentiate the source of the data during analog recording.

**Procainamide infusion.** In the three patients with coronary disease, procainamide was given for the purpose of testing its effects on inducibility of ventricular tachycardia. In neither of the patients with chronic atrial fibrillation did atrial fibrillation terminate as a result of this infusion. In the remaining patient with coronary disease, atrial fibrillation was terminated as a result of the infusion. In the five patients without coronary disease, procainamide was given for the purpose of terminating induced atrial fibrillation. In these patients, at least 5 min were allowed to pass with the patient in atrial fibrillation before beginning the drug infusion. Procainamide hydrochloride was given intravenously at a rate of 50 mg/min through an infusion pump (Imed Corp., San Diego, CA) until sinus rhythm was restored or a total of 1 g had been given. The infusion had to be interrupted briefly in two patients (1 min and 2 min, respectively) because of modest hypotension. Serum levels of procainamide were drawn routinely at the end of electrophysiologic testing and ranged from 3.5 to 20.3 μg/ml (mean ± SD, 7.2 ± 5.6 μg/ml).

**Preprocessing.** Data that were stored on tape were played back through an antialiasing filter with a cut-off frequency of 200 Hz. Data were given appropriate gain and digitized at 1200 Hz. Surface leads II and V1, and the unfiltered and filtered intra-atrial leads were digitized simultaneously. Three separate records were digitized for each trial of procainamide (11 trials for eight patients). The “procainamide” record consisted of one full minute of continuous data taken before administration of procainamide. The “entire” record consisted of 5120 point (4.27 sec) segments taken once every 50 sec beginning as soon as possible after the onset of atrial fibrillation (preceding procainamide infusion) and ending 1 min after conversion to sinus rhythm (or 10 min after infusion was complete for those patients whose arrhythmias did not convert). Finally, the “postprocainamide” segment consisted of one full minute of continuous data immediately preceding conversion followed by 30 sec of data after conversion to sinus rhythm. For those patients whose arrhythmias did not convert, the “postprocainamide” segment consisted of 90 sec of continuous data immediately after the end of the infusion. All three records were then divided into 5120 point (4.27 sec) segments for analysis. All data analysis was performed on a Masscomp MCS-563 computer system (Massachusetts Computer; Littleton, MA).

**Power spectrum analysis.** The unfiltered 4.27 sec data segments of all three records were analyzed in all 11 trials of procainamide. The data were filtered digitally at 60 Hz with a three-pole, low-pass, Butterworth filter. Data were then reduced to 512 points by extracting every tenth point and padded symmetrically with zeroes to give 1024 point segments. Such reduction gives an effective sampling rate of 120 Hz, which in terms of sampling theory is adequate for data that have already been filtered to 60 Hz. A 1024 point fast-Fourier transform was then performed on each data segment, and the information in the 1 to 60 Hz band was saved to give a power spectrum with resolution of 0.12 Hz. The median frequency in the 2 to 9 Hz band was then determined for each data segment. This band was chosen because previous studies in our laboratory suggest that this region contains most of the power during atrial fibrillation. The median frequency was defined as that frequency in the 2 to 9 Hz band at which half the power in this band was below and half the power was above.

**Atrial rate.** The filtered 4.27 sec data segments of all three records were analyzed in all 11 trials of procainamide. The data were reduced to 1024 points by extracting every fifth point. The mean of the data was determined and subtracted from each data point. Then the absolute value of each data point was calculated and used for the atrial rate calculation. The point of maximum amplitude was located in each segment, and an amplitude threshold was set to 10% of that maximum amplitude. Each time the signal crossed above the threshold, the maximum peak in the next 50 msec was determined and labeled an electrogram. When an electrogram occurred, detection was inhibited for 50 msec to prevent detection of multiple peaks in one electrogram and still allow for maximum detectable rates of 1200 beats/min. Atrial cycle length was defined as the time that elapsed between detected electrograms. The average atrial cycle length was determined from all detected electrograms in a segment, and the atrial rate was then found by taking the inverse of the average atrial cycle length.

**Amplitude probability density function.** The filtered 4.27 sec data segments of all three records were analyzed in all 11 trials of procainamide. The data were reduced to 1024 points by extracting every fifth point. Data were then normalized so that the range of amplitudes was 1000 units with zero mean. When a signal consists of an “isoelectric” line with discrete positive or negative electrograms, subtracting the mean from the signal (which is done during any high-pass filtering) will result in the “isoelectric” line moving to the opposite side of zero than the electrograms. Consequently, most data points (those on the “isoelectric” line) will lie to one side of zero. Thus, instead of simply determining the percentage of points that lay within the 25 to +25 unit interval centered on zero, we chose to use the following sliding-bucket algorithm. The data points were sorted according to amplitude. The percentage of the total points that lay within in each five-unit amplitude interval from 100 to +100 (i.e., 100 to 95, 95 to 90, . . . , +95 to +100) was then determined. The five-unit interval containing the largest percentage of points was then determined (B1). Next, the 10-unit interval containing the largest percentage of points and containing B1 was determined (B2). Similarly, the 20-unit interval containing the largest percentage of points and containing B2 was determined (B3). Finally, the 50-unit interval containing the largest percentage of points and containing B3 was determined. Density was defined as the percentage of points in this 50-unit interval.

**Definitions.** Atrial fibrillation was judged to be present if standard surface electrocardiographic criteria were met. The effect of procainamide on detection of atrial fibrillation from
intra-atrial electrograms was determined using previously published criteria. Arzbaecher et al. have defined an atrial rate cutoff of 330 beats/min for detection of atrial fibrillation. Our laboratory has defined atrial rate, percent power, and density thresholds of > 320 beats/min, > 27%, and < 78%, respectively, for atrial fibrillation. Each preprocainamide and postprocainamide segment was analyzed for atrial rate, percent power in the 4 to 9 Hz band, and density. The values for these variables were then compared with the previously published criteria. Although median frequency was used to examine changes in the frequency characteristics of the signal during procainamide, this variable has not previously been tested as a detection criterion for atrial fibrillation. Therefore percent power measurements were used instead for the purpose of testing detection algorithms.

Statistics. An unpaired t test was used to compare the preprocainamide mean to the postprocainamide mean for each variable in all 11 trials. To examine the effects of procainamide throughout the infusion, a least-squares linear regression was performed on each variable (median frequency, rate, and density) vs time for those segments of the "entire" record that were between the beginning of infusion of procainamide and the conversion to sinus rhythm but not including segments with sinus rhythm itself. For the patients whose arrhythmias did not convert, the segments between infusion of procainamide and the end of infusion were used instead.

Results

There were 11 trials of procainamide infusion during atrial fibrillation. In nine of these 11 trials, atrial fibrillation was converted to sinus rhythm (figure 1). The duration of atrial fibrillation in these nine trials ranged from 12 to 39 min (mean 26) from onset to termination. The amount of procainamide infused at the time of termination ranged from 250 to 1000 mg (mean 617). We observed a marked decrease in electrogram amplitude during atrial fibrillation compared with that during sinus rhythm.

Power spectrum analysis. As previously reported by our laboratory, the power spectra of the intra-atrial electrograms during atrial fibrillation typically exhibited a large peak of power in the 2 to 9 Hz frequency band and very little power outside of this region. The power spectra appeared to be band limited and lacked harmonic components. During infusion of procainamide, the power spectra were similar in appearance but there was a tendency for the large peak of power to shift toward a lower frequency. This shift in the large peak of power could be measured by the shift in median frequency. Figure 2, A, illustrates the decrease in median frequency during the drug infusion for one trial of this study. This decrease in median frequency occurred in each of the 11 trials during administration of procainamide as is illustrated in figure 3, A (p < .01). The median frequency for the 88 preprocainamide segments (11 trials × 8 segments) ranged from 3.63 to 7.85 Hz (mean 5.50 ± 1.22), and the median frequency for the 88 postprocainamide segments ranged from 2.70 to 6.21 Hz (mean 4.24 ± 0.99) (p < .0005).

When the entire records were analyzed, the decrease in median frequency was gradual, and there appeared to be a linear trend to this decrease in some trials. Thus, a linear regression of median frequency vs time was performed to examine the effects of procainamide throughout the infusion. In each of the 11 trials, the slope was negative. The slopes ranged from −0.16 to −0.0052 Hz/min (mean −0.074 ± 0.046). The negative slope reached statistical significance (p < .05) in nine of the 11 trials.

Atrial rate. As has been described by others, there was marked baseline variability in the measured atrial rate. Administration of procainamide did not appear to alter this variability. However, the atrial rate generally slowed during the infusion. Figure 2, B, demonstrates this decrease in rate with time during infusion of procainamide for one trial of the study. The atrial rate decreased in 10 of 11 trials during administration of procainamide, including all nine trials in which atrial fibrillation converted to sinus rhythm (figure 3, B). The decrease in atrial rate reached statistical significance (p < .05) in eight of 11 trials. The atrial rate for the 88 preprocainamide segments ranged from 283 to 726 beats/min (mean 498 ± 97), and the atrial rate for the 88 postprocainamide segments ranged from 60 to 714 beats/min (mean 356 ± 146) (p < .005).
there was a slight increase in density, suggesting that the signal had developed more discrete electrograms and a more isoelectric baseline. Figure 2, C, demonstrates a typical increase in density during administration of procainamide for one trial of the study. An increase in density occurred in 10 of 11 trials after infusion of procainamide (figure 3, C). The increase in density reached statistical significance (p < .05) in nine of 11 trials. For the 88 preprocainamide segments, the density ranged from 20.2% to 79.7% (58.3 ± 13.9%), and the density for the 88 postprocainamide segments ranged from 27.9% to 90.9% (69.1 ± 15.0%) (p < .005).

As for median frequency and atrial rate, a linear regression was performed to track the changes in density throughout the infusion of procainamide. The slope was positive in nine of the 11 trials and negative in the

FIGURE 2. Examples (from different patients) of changes in median frequency (M.F.) (A), atrial rate (B), and density (C) during infusion of procainamide. "P" marks the beginning of infusion.

Because of the magnitude of variability in the measured atrial rate, the decrease in atrial rate during the entire record did not follow such a linear trend as did median frequency. A linear regression was performed to examine the changes in atrial rate throughout infusion of procainamide. The slope was negative in nine of 10 trials and positive in one trial. The slopes ranged from −47.4 to 1.54 beats/min² (mean −12.6 ± 16.0). This negative slope reached statistical significance (p < .05) in five of 11 trials.

Density. Density is a measure of the amount of time that the signal spends near the isoelectric line. As reported previously by our laboratory, density was significantly less during atrial fibrillation than during sinus rhythm. When procainamide was administered,

FIGURE 3. Preprocainamide and postprocainamide values for average median frequency (M.F.) (A), average atrial rate (B), and average density (C) for each trial of procainamide. The mean ± 1 SD for eight data segments is indicated.
remaining two trials. The slopes ranged from $-0.576\%$/min to 2.54\%$/min (0.56 \pm 0.82\%$/min). The positive slope reached statistical significance ($p < .05$) in three of 11 trials.

Reproducibility. Two patients who received multiple infusions of procainamide during atrial fibrillation showed consistent changes in median frequency, atrial rate, and density from trial to trial. In one patient who received three separate infusions during one study, the average median frequency decreased from 4.32 to 2.99, 4.31 to 3.03, and 3.88 to 3.32 Hz during the first, second, and third trials, respectively. Similarly, the average atrial rate decreased from 585 to 263, 482 to 346, and 520 to 263 beats/min in the first, second, and third trials, respectively. Average density increased in all three trials from 50.7\% to 73.1\%, 62.1\% to 72.9\%, and 61.8\% to 76.1\%.

A second patient received procainamide during atrial fibrillation during two separate studies. This patient's average median frequency decreased during infusion of procainamide from 5.10 to 3.54 Hz and from 4.54 to 3.91 Hz in the first and second trials, respectively. The average rate also decreased in the first and second trials, from 537 to 212 beats/min and from 592 to 533 beats/min, respectively. Furthermore, the average density increased from 55.2\% to 83.4\% in the first trial and from 43.3\% to 61.0\% in the second trial.

Potential drug-device interactions. In this study, there were a total of 88 preprocainamide records and 88 postprocainamide records analyzed for atrial rate, percent power in the 4 to 9 Hz band (in place of median frequency to allow comparison to previously published data), and density. Of the preprocainamide segments, only two of 88 (2.3\%) had rates below 320 beats/min (and 330 beats/min). In contrast, for the postprocainamide segments, 44 of 88 (50\%) had rates below 320 beats/min (and 45 of 88 [51\%] < 330 beats/min), and yet the ECG and electrograms continued to meet standard morphologic criteria for atrial fibrillation as opposed to atrial flutter or atrial tachycardia6, 8 (figure 4). Similarly, only five of 88 preprocainamide segments (5.7\%) had less than 27\% power in the 4 to 9 Hz band, but 32 of 88 postprocainamide segments (36.4\%) had less than 27\% power in the 4 to 9 Hz band. Of the preprocainamide segments, only three of 88 (3.4\%) exceeded the 78\% density threshold for atrial fibrillation, but 25 of the 88 postprocainamide segments (28.4\%) had a density greater than 78\%. Thus it was observed that infusion of procainamide resulted in changes in atrial electrograms to the degree that the proposed algorithms for atrial fibrillation would fail (figure 5).

A minority of the segments that failed to meet threshold criteria during infusion of procainamide showed discrete atrial activation resembling atrial flutter in the electrogram and/or surface recordings (figure 6). This flutterlike activity was more discrete and regular in timing than classic atrial fibrillation. However, the baseline was not isoelectric, and the morphology and timing of the discrete electrograms were not constant, as should be the case for atrial flutter. Wells et al.8 describe this type of intra-atrial recording as type I atrial fibrillation. In no instance during this study did we observe atrial fibrillation to convert to classic atrial flutter or atrioventricular reentrant tachycardia with the infusion of procainamide.

Discussion
To function appropriately, an antitachycardia device must accomplish two ends. First, it must be capable of administering effective therapy for a cardiac arrhythmia. Second, it must be capable of recognizing the necessity of administering such therapy. This requires algorithms with excellent sensitivity and specificity in
recognizing cardiac arrhythmias. In addition, these algorithms must be robust in the face of changing clinical conditions.

Since drugs are currently the mainstay of antiarrhythmic therapy, many patients who are candidates for implanted antitachycardia devices may be taking one or more antiarrhythmic drugs concurrently. For example, 48 of 70 patients with implanted cardioverter/defibrillators reported by Echt et al. were taking concomitant antiarrhythmic drug therapy. In addition, variations in drug pharmacokinetics and patient compliance will insure that drug levels (and presumably effects on electrograms) will vary greatly from time to time in any one patient. Furthermore, the time relationship of plasma drug levels to effects on the electrograms seems somewhat unpredictable. Liem et al. have reported that the effect of procainamide on QRS complex duration closely followed plasma levels in six of nine patients, but delays of 3, 10, and 18 min, respectively, were noted in the remaining three patients. Since drug side effects are common, one can anticipate that changes in the drug regimen will be frequent. Therefore it seems reasonable to assume that a successful tachycardia recognition algorithm must be immune to drug-induced changes in electrogram characteristics. Drug-device interactions have been recently reviewed by Reiffel et al. A few instances of antitachycardia device failure due to drug effects have been reported. However, this has not previously been studied in a systematic manner.

Numerous clinical studies have shown that procainamide is often successful in converting atrial fibrillation to sinus rhythm in human subjects. The efficacy of procainamide in converting atrial fibrillation to sinus rhythm appears to be correlated with the duration of atrial fibrillation before drug administration. Although the exact mechanism by which procainamide terminates atrial fibrillation is not well understood, the electrophysiologic changes that this drug induces in human atrial tissue include depression of excitability, slowing of conduction, and prolongation of refrac-

FIGURE 5. Failure to meet threshold criteria for atrial fibrillation. Illustrated are the percent of 4.27 sec data segments that failed to meet threshold criteria for atrial rate, percent power, and density before and after infusion of procainamide. The two rate criteria are those published by Slocum et al. and Arzbaecher et al., respectively.

FIGURE 6. Flutterlike atrial activity during atrial fibrillation. These surface (II, V1) and intra-atrial recordings (HRAF, HRAU) illustrate typical flutterlike activity as seen in a few segments after infusion of procainamide. Some suggestion of discrete atrial activity is noted in the surface recordings; however, this activity is not consistent in timing. Although discrete electrograms exist in the intra-atrial recordings, the timing and morphology of these discrete complexes are not regular and the baseline is not isoelectric.
toriness. How the electrophysiologic effects of procainamide influence the intra-atrial electrogram signal was one focus of this study. Previously, researchers have reported a definite slowing in rate and a coarsening and widening of the fibrillatory waves in the surface ECG during administration of procainamide.\(^{14, 15, 19}\) We demonstrated that for intra-atrial electrograms, atrial rate slowed, amplitude probability density increased, and median frequency decreased during infusion of procainamide and that these changes had profound consequences on proposed rhythm detection algorithms.

Although percent power in the 4 to 9 Hz band was used previously by our laboratory for detection criteria, this measurement failed to measure the shift in the large peak of power after infusion of procainamide. For example, a large peak that originates at 7 Hz and then shifts to 6 Hz after procainamide remains in the 4 to 9 Hz band and does not alter percent power, despite the dramatic change in the frequency content of the signal.

Atrial rate slowed in 10 of 11 trials but showed marked baseline variability that continued throughout the drug infusion. This variability in the actual signal has been described by others.\(^{8}\) Often, the intra-atrial recordings showed episodes of discrete, large-amplitude electrograms superimposed on low-amplitude, high-frequency undulations. These were mixed with episodes lacking in any form of discrete activity (figure 7). Thus the lack of a periodic, distinct activation complex makes atrial "rate" of uncertain meaning during atrial fibrillation. The rate algorithm used in this study is highly sensitive to the threshold chosen for electrogram detection.\(^{4}\) A single, very large-amplitude electrogram could give rise to low measured rates because of an inappropriate threshold set for the remainder of the segment. Thus a more robust rate algorithm may be required if rate is to be used.

Although Kerr and Mason\(^{23}\) have reported that the mean amplitude of atrial electrograms does not change from sinus rhythm to atrial flutter of fibrillation, we did not find this to be the case. On the contrary, electrogram amplitude was substantially decreased during atrial fibrillation and increased again with the restoration of sinus rhythm. Since measured atrial rate is critically dependent on the threshold chosen for electrogram detection,\(^{4, 8}\) a device must have the capability to adjust automatically to this amplitude change if a rate algorithm is used to differentiate these rhythms. In this study, a new detection threshold was chosen for each
segment; thus changes in amplitude from atrial fibrillation to sinus rhythm would have no effect on the measured rate.

The amplitude probability density function measures the distribution of the signal amplitude about the isoelectric region. In the case of sinus rhythm, most of the data points lie near the baseline, whereas a small percentage of points lie at the extremities (those points that make up the discrete atrial complex). Thus, the density of points about zero should be large. Conversely, during atrial fibrillation, there is usually no isoelectric baseline, and most of the points are scattered to either side of the isoelectric region. In this study, there was an increase in density in 10 of 11 trials during infusion of procainamide, but the change was of small magnitude. How such a change in the amplitude probability density function relates to the underlying mechanism is not clear, but could reflect fewer wavelets, each involving a larger atrial mass within the field recorded by the bipole, than before drug infusion.

A highly significant and troubling result of this study is the marked increase in the number of segments that failed to meet previously published criteria for atrial fibrillation during infusion of procainamide compared with the number of segments before the drug infusion. Such an increase suggests that antiarrhythmic drugs, at least in high doses, may alter signal characteristics to the degree that many current detection criteria would fail.

Although this is, to our knowledge, the first thorough examination of the effect of a specific antiarrhythmic drug on specific detection algorithms, there is reason to believe that our findings will prove generally applicable. We believe that similar findings must be expected with other drugs and other algorithms for arrhythmia detection. Any algorithm that depends on signal processing techniques must use time-domain criteria, frequency-domain criteria, or both to characterize waveforms. Our data demonstrate that both time- and frequency-domain characteristics change with infusion of procainamide. In addition, preliminary data suggest that the same potential drug-device interactions that we have demonstrated would be found for atrial fibrillation in dogs, 3, 7, 24 for ventricular tachycardia, 25 for different electrode configurations, 24 and for other drugs. 26 We therefore predict from our data that algorithms that are robust in the face of such changes will be required to prevent serious drug-device interactions.

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