Correction for QT/RR Hysteresis in the Assessment of Drug-Induced QTc Changes—Cardiac Safety of Gadobutrol

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Background: The so-called thorough QT/QTc (TQT) studies required for every new pharmaceutical compound are negative if upper single-sided 95% confidence interval (CI) of placebo and baseline corrected QTc prolongation is <10 ms. This tight requirement has many methodological implications. If the investigated drug has a fast action and ECGs cannot be obtained at stable heart rates, QT/RR hysteresis correction is needed.

Methods: This was used in a TQT study of gadobutrol. The TQT study was a randomized double-blind five-times crossover study of three doses of gadobutrol (0.1, 0.3, and 0.5 mmol/kg) that was placebo and positive effect controlled (moxifloxacin 400 mg). The study enrolled 50 healthy subjects with data of all periods. QT/RR hysteresis was assessed from prestudy exercise test ECGs. Among others, comparisons were made between population heart rate correction without hysteresis considerations and combined population heart rate and hysteresis correction.

Results: The highest heart rate increase (placebo and baseline controlled) of 13.1 beats per minute (90% CI 9.9–16.4) occurred 1 minute after the administration of the highest dose of gadobutrol. Without hysteresis consideration, the highest $\Delta\Delta\text{QTc}$ were 9.91 ms (90% CI 8.01–11.81) while with hysteresis correction, these values were 7.62 ms (90% CI 6.37–8.87), thus turning a marginally positive TQT study into a negative finding.

Conclusion: Hence, omitting hysteresis correction from episodes of fast heart rate changes may lead to incorrect conclusions. Despite substantial rate acceleration, accurate hysteresis correction confirms that gadobutrol does not have any effects on cardiac repolarization that would be within the limits of regulatory relevance.

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drug-induced QT prolongation; heart rate correction; clinical QT study; QT/RR hysteresis

INTRODUCTION

Present regulatory guidance requires all new pharmaceutical compounds to be investigated for potential influence on cardiac repolarization to avoid drugs causing torsade de pointes (TdP) tachycardia.¹ Although it is well recognized that drug-induced QT and QTc interval prolongation is only an indirect and not particularly specific indication of torsadogenic toxicity, no superior clinical predictors are presently available.² Therefore, the so-called thorough QT/QTc is required in investigating QTc interval changes at therapeutic and suprather-

apeutic doses of new compounds.¹ Regulatory consensus agrees that drugs that are found not to prolong QTc interval or to prolong it only a little will be associated with TdP tachycardia with such low frequency (e.g., well below 1 case per 1 million exposures) that the danger of proarrhythmic toxicity does not need to be considered for regulatory decisions. The "little" QTc prolongation is defined as the maximum baseline- and placebo-corrected QTc prolongation with the upper 95% single-sided confidence interval not exceeding 10 ms.¹

This tight criterion has many methodological implications for the conduct of the thorough QT/QTc

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studies as well as for the accuracy of electrocardiographic (ECG) measurements. Among others, it is well recognized that inaccurate heart rate correction of the QT interval measurements may lead to both false positive and false negative findings. Utility of Bazett's formula has now been practically abandoned even when investigating drugs that do not lead to treatment-related heart rate changes. The necessity of using individualized heart rate correction is well known for studies of drugs that do lead to systematic heart rate acceleration or deceleration.³ Methodology of heart rate correction therefore recently received substantial attention.^{4–6}

It has also been experimentally verified that obtaining QT interval measurements that are preceded by stable heart rates reduces the variability of QTc data by avoiding the effects of the so-called QT/RR hysteresis.^{7,8} Recently, we have reported that even in these situations, correction for QT/RR hysteresis reduces the QTc variability even further thus allowing the thorough QT/QTc studies to be smaller and more economical.⁹

There are, however, situations when the investigated drug has such a fast action on heart rate that the QT interval measurements of interest cannot be preceded by stable heart rate episodes of sufficient duration. In such situations, the correction for QT/RR hysteresis is potentially of paramount importance since omitting it may lead to erroneous regulatory conclusions. This article is aimed at demonstrating such a situation.

METHODS

Gadobutrol is a gadolinium-based paramagnetic contrast agent for magnetic resonance imaging.¹⁰ The drug is administered intravenously. It is rapidly distributed in the extracellular space and is eliminated unchanged in urine. No metabolites are detectable in plasma or urine.^{10,11}

Thorough QT/QTc Study

Cardiovascular safety of gadobutrol injection with particular attention to ECG changes indicative of potential torsadogenic toxicity was investigated in a dedicated clinical study. The study was a five-times crossover trial involving five periods of 24-hour continuous ECG recordings. Each subject received a total of five injections: three injections of gadobutrol (0.1, 0.3, and 0.5 mmol/kg in three sep-

arate intraindividual treatment periods), one injection of placebo, and one injection of a positive control (moxifloxacin 400 mg administered as 1 hour infusion^{12,14}). The injections of gadobutrol and of placebo lasted 1–2 minutes. The periods were separated by appropriate washouts. Apart from moxifloxacin period, treatment was double blinded. All periods were randomly assigned and the ECG records were collected in a fully blinded format. The study was performed at Parexel clinical unit at Baltimore, MD. The conduct was approved by institutional Ethics Committee and all participants gave written informed consent.

Prebaseline Study of QT/RR Relationship

Before the first period of randomized treatment, all study subjects underwent a prebaseline investigation with a $3\frac{1}{4}$ hours continuous 12-lead ECG recording. The recording started with a 45-minute rest period. Subsequently, the ECGs were obtained during indoor cycling 10 minutes with 50 watts workload, 10 minutes with 75 watts workload, and 10 minutes with 100 watts workload. The same exercise protocol was repeated after 45 minutes of rest and then followed by another period of 45 minutes rest. During the rest periods, the subjects were in supine position; upright sitting positions were used during cycling.

Data Extraction from ECG Recordings

The continuous 12-lead ECG recordings of the study were obtained using Mortara H Scribe system (Mortara Instrument, Milwaukee, WI) with raw data sampled at 180 Hz. Since this resolution was considered inadequate for accurate RR and QT interval measurements, the raw data were cubic spline interpolated and resampled, allowing interval measurement with 1 ms precision.

The prebaseline exercise test recordings were divided into nonoverlapping periods of 100-second duration and within each such period, a 10-second segment was identified with the lowest noise contents. The noise contents were measured objectively by using previously described technology.¹⁵

In each on-treatment recording, 21 periods of interests were identified according to times relative to the end of drug administration. The times of these sections were (in minutes): –80 to –75; –75 to –70; –70 to –65; –65 to –60; 0 to 0.5; 1 to 1.5; 2 to 3; 4 to 5; 6 to 7; 8 to 9; 10 to 11; 12

to 13; 15 to 17; 30 to 35; 60 to 65; 120 to 125; 180 to 185; 240 to 245; 360 to 365; 480 to 485; and 1315 to 1325. The first four of these sections represented the pretreatment baseline data while the subsequent 17 sections were timed to the expected effects of the investigated compounds. In each of these sections, three nonoverlapping 10-second ECG segments were identified, which again had the lowest noise contents within the given section.

Finally, further ECG segments were selected from placebo recordings to characterize individual QT/RR patterns uninfluenced by active treatment. These patterns were subsequently used for the purposes of individualized heart rate correction (see further). Accurate QT/RR pattern characterization must include sufficient heart rate range with comprehensive sampling between the slowest and fastest rates. This is not achievable by using only recordings obtained in prespecified time windows since their heart rates do not necessarily differ sufficiently. Therefore, all 10-second ECG segments preceded by >120 seconds of stable heart rate (variability < ± 2 beats per minute) were found in the daytime portions of placebo recordings. These were sorted according to the preceding stable rate and divided into 200 bins as equidistant as possible in the underlying heart rate. In each bin, the 10-second ECG segment with the lowest noise contents was selected for accurate measurement. The restriction to daytime portions of the recordings was needed because of the known day-night differences in QT/RR patterns¹³ and because all the study data-points (as described earlier) occurred during daytime hours.

ECG Measurement

Each selected 10-second ECG segment was filtered and its baseline wander was removed. (Study-specific filtering and baseline removal technique was used.) From these signals, medium representative beats were constructed and QT interval was measured using an advanced version of pattern-matching algorithm.

In each ECG, the measurement triggers were visually checked and, where necessary, manually corrected by two independent cardiologists. These visual checks and measurement corrections were performed on computer screen in the median beats with superimposed images of all 12 leads. The car-

diologists were also permitted to declare an ECG segment nonmeasurable.

The results of these measurement checks by the two cardiologists were compared and those ECG identified in which the cardiologists differed either in their decision on measurability or in the QT interval measurement by >6 ms. These ECGs were returned to the same pair of cardiologists for repeated verification. Otherwise, the positions of the Q onset and T offset triggers were averaged. After the second measurement, the results provided by the two cardiologists were again compared and in cases where they still disagreed were reconciled by a senior cardiologist. All the measurements of the study were performed by the same personnel.

After the QT interval measurements were completed and reconciled on the median representative beats, the Q-onset and T-offset triggers were projected into individual beats of the 10-second ECG segment by using pattern matching.¹⁶ The projection was visually checked on computer screen and manually corrected where necessary.

QT/RR Hysteresis Correction

In all 10-second segments selected for accurate QT interval measurements, the sequences of RR intervals were obtained covering both the contents of the 10-second segment as well as the history of 250 RR intervals preceding the selected 10-second segment.

Using an optimized version of the previously published technology,¹⁷ individual models of QT/RR hysteresis were calculated from the data of QT durations and their RR history taken from pre-baseline exercise tests. In each subject, the QT/RR hysteresis was characterized by a numerical parameter λ that defined the weighted average of the RR intervals preceding the QT interval measurement. Following the previously published methodology, the following formula was used to calculate the RR interval value RR^H that represented the heart rate for which the measured QT interval should be corrected:

$$RR^H = \sum_{i=1 \dots n} (e^{-\lambda(i-1)/n} - e^{-\lambda i/n}) / (1 - e^{-\lambda}) RR_i$$

where RR_i is the i th RR interval preceding the QT interval measurement and n is the duration of the known history of the measurement (see the Appendix for technical details).

Heart Rate Correction

Active drug uninfluenced QT/RR patterns were obtained in each subject from the 200 ECG segments selected by scanning the stable heart rate periods of the placebo recording. In each subject, this QT/RR pattern was converted into an individualized heart rate correction formula including QT/RR curvature optimization.^{18,19} These individualized corrections were subsequently applied to all on-treatment QT interval measurements.

Subject specific heart rate correction was also simplified by optimizing the coefficient of the log/log parabolic correction model, that is by obtaining individual specific coefficients for the heart rate correction formula of $QT_c = QT/RR^\alpha$.²⁰ Using the same principles, the population optimized heart rate correction was derived utilizing the median value individual-specific heart rate correction coefficients α .

Combinations of Heart Rate and Hysteresis Corrections

In order to study the effects of QT/RR hysteresis corrections and its combination with heart rate correction, the data of the study were evaluated using 12 different modes. Specifically, three different QT/RR hysteresis corrections, that is:

- (a) No hysteresis considered by relating each QT interval measurement to the average of RR intervals obtained in the same 10-second ECG segment,
- (b) Individual hysteresis correction with individual-specific λ coefficients, and
- (c) Population hysteresis correction using the median λ value of all the study subjects,

Where combined with four different heart rate correction possibilities (per analytical protocol of the study), namely:

- (a) Individualized correction including individual specific curvature optimization,
- (b) Individualized optimization of a fixed mathematical formula of the log-log model,
- (c) Population correction using the median value of the individual specific correction coefficients of the fixed mathematical form of the log-log model, and

- (d) Fridericia formula $QT_c = QT/RR^{1/3}$.²¹ (Fridericia correction was added to the analytical protocol of the study for purely historical reasons. The assessment of the hysteresis involves data-driven optimization of the heart rate correction and in this sense, going back to "ad hoc" Fridericia correction is counterproductive.)

Since the results were generally consistent across this spectrum of correction possibilities, only two of these combinations are presented in this text, namely the combination of population heart rate correction combined either with no hysteresis or with the population hysteresis correction (comparison of these combinations allows concentrating on the effect of the hysteresis correction).

The QT_c calculations were made for individual beats of the measured 10-second ECG segments and subsequently averaged.

Data Evaluation and Statistics

As it is usual in the evaluation of thorough QT/QT_c studies,¹ the evaluation of the trial was based on QT_c changes from baseline at separate data points of the study (ΔQT_c values) and on evaluation of intra subject differences between ΔQT_c on active treatment and corresponding ΔQT_c values on placebo ($\Delta \Delta QT_c$ values).

The evaluation of ΔQT_c and $\Delta \Delta QT_c$ values was based on population means calculated together with dual sided 90% confidence intervals (i.e., single-sided 95% confidence intervals) assuming normal distribution. This is standard implementation of the so-called intersection union test that is prescribed for the thorough QT/QT_c studies.

RESULTS

The study involved 81 normal healthy volunteers who completed the prebaseline exercise test. The results presented here are derived from a population of 50 subjects (mean age 35.28 ± 9.21 , range 19–60 years, 25 women) for whom completed data of all five on-treatment periods were available.

The assessment of individual QT/RR hysteresis corrections led to λ parameters ranging between 1.611 and 7.029 with median value of 4.966, which was used for the population hysteresis correction. The individual α coefficients of the heart rate correction model $QT_c = QT/RR^\alpha$ ranged between 0.1428 and 0.4219 with the median value of 0.3023,

Figure 1. For individual data points of the study, the figure shows actual values of heart rate (top left panel), their differences from baseline (bottom left panel), their differences from placebo (top right panel), and their differences from baseline and placebo (bottom right panel). The actual values are shown as means $\pm$ standard error of mean (SEM), the other panels show the data as means with 90% confidence intervals (CI).

which was used for the population heart rate correction.

Figure 1 shows heart rate changes during the individual treatment periods. While there were no appreciable heart rate changes on placebo and on the lowest dose of gadobutrol, there were heart rate increases during the other treatment periods with the highest increase on the high dose of gadobutrol. However, while the heart rate increase on moxifloxacin positive control was gradual during the infusion (interim data during the infusion are not presented here), the heart rate increases on gadobutrol were rapid during the short injections. This is not surprising as the effect is known with high-osmolarity injections. The largest heart rate increase (compared to placebo and baseline) on the highest dose of gadobutrol occurred 1 minute after the end of drug administration and was 13.1 beats per minute (90% confidence interval 9.9–16.4 beats per minute).

Figures 2 and 3 shows the QTc changes during the individual treatment periods. Figure 2 shows these changes calculated with population-specific

heart rate correction without any hysteresis considerations while Figure 3 shows recalculations that involved both population heart rate correction and population hysteresis correction. The differences between the two results are in agreement with the fast heart rate changes shown in the Figure 1. While the numerical differences between the two results are not very large, the comparison of the results obtained with $\Delta\Delta\text{QTc}$ evaluation shows that while the results calculated without hysteresis correction resulted in a marginally positive thorough QT/QTc study in which the QTc changes on the highest dose of gadobutrol were well above the regulatory threshold (maximum mean $\Delta\Delta\text{QTc}$ on the highest dose of gadobutrol of 9.91 ms; 90% confidence interval of 8.01–11.81 ms), the recalculation that involved the hysteresis correction leads to a fully negative thorough QT/QTc study with the upper confidence interval of QTc change on the highest dose of gadobutrol well below the 10 ms threshold (maximum mean $\Delta\Delta\text{QTc}$ on the highest dose of gadobutrol of 7.62 ms; 90% confidence interval of 6.37–8.87 ms).

Figure 2. QTc values obtained with population heart rate correction without any QT/RR hysteresis correction. The layout of the figure is the same as in Figure 1.

Figures 2 and 3 also show that the study demonstrated ECG assay sensitivity. For 6 hours after the moxifloxacin infusion, the lower 90% confidence intervals of $\Delta\Delta\text{QTc}$ were all above 5 ms prolongation. The figures also show that since moxifloxacin infusion does not lead to any systematically fast heart rate changes, the effect of hysteresis correction is less obvious although the trend of moxifloxacin effect is more stable if hysteresis correction is used.

DISCUSSION

The results of the study demonstrate clearly that omitting hysteresis correction from episodes of fast heart rate changes may lead to imprecise conclusions on QTc interval prolongation especially when clinical and regulatory interpretation of the data needs to be distinguished. While a clinical view would likely conclude that gadobutrol is free of repolarization effects with both sets of results, the regulatory assessment rightly needs to be more rigorous utilizing consistent and prespecified thresholds.¹

Physiologically, the result of the study is not surprising. When QT interval is measured while heart rate is rapidly accelerating, it is not only influenced by the simultaneously measured fast heart rate but also by the history of the preceding slower rate. In other words, during such an episode, QT interval cannot be corrected for the simultaneously measured heart rate because it has still not adapted to the elevated level of rate. The previous slow rate needs to be considered since it still influences the longer QT interval duration.

The extent of the difference between the hysteresis omitting and hysteresis incorporating QTc values that we have observed in this study is in good agreement with previous experimental and clinical studies that investigated QT/RR hysteresis. In seminal study on the adaptation of action potential durations to abrupt pacing rate changes, Franz et al. reported that this adaptation was completed after approximately 2 minutes.²² Similarly, Lau et al. reported an approximately 2 minute duration of QT interval hysteresis when provoked by abrupt changes in cardiac pacing rates.²³ Consistent with these findings, we have observed the effect of the

Figure 3. QTc values obtained with population heart rate correction combined with population QT/RR hysteresis correction. The layout of the figure is the same as in Figure 1.

hysteresis correction within the first minutes after gadolinium injections. Also, the individual parameters of hysteresis models corresponded to the 95% QT interval adaptation being reached after approximately 150 RR intervals that again corresponds to the previously reported time scale.

Even after correcting the QT data for rate and hysteresis, we noticed some marginal and dose related QT prolongation shortly after gadobutrol injections. This is most likely linked to the volume changes due to drug administration, possibly even more so for drugs with osmolality higher than that of plasma. Indeed, QTc prolongation was recently reported after placebo infusions.²⁴ The mechanisms for this are not known but it seems plausible to speculate that they are related to autonomic influences triggered by the volume changes.

In addition to the methodological conclusions, the study therefore permits to conclude that gadobutrol administration does not have any effects on cardiac repolarization that would be not only of clinical but also of regulatory relevance.

This is not only supported by the negative thorough QT/QTc study result obtained with the proper hysteresis correction but also by studies of the relationship between the dynamics of observed minimum QTc changes and the dynamics of gadobutrol plasma levels that we have not presented in this text. This is in good agreement with the available clinical experience with the drug.²⁵

Several limitations of this study also need to be considered. The individual QT/RR hysteresis parameters were assessed from recordings obtained during prebaseline exercise tests. While the exercise tests guaranteed sufficient heart rate changes for proper hysteresis modeling, the study did not investigate whether such extra exercise test data are needed. Variable heart rate changes occur under a variety of conditions and it seems plausible as well as more practical to assess hysteresis models from standard long-term baseline recordings. Eliminating the necessity of an exercise test for hysteresis assessment would clearly make the technology more practical. We have also used hysteresis models expressing the heart rate history in counts of

RR intervals. It has been previously observed that this is practically equivalent to the expression of the history in terms of time units but we have not investigated this approach in this study. Several of the numerical parameters used during ECG processing (e.g., the 6 ms agreement limit for separate readings by two different cardiologists) were derived from previous experience as well as reflecting ECG measurement practicality. We are unable to comment on the influence of these particular parameter settings on the overall ECG measurement process. Likewise, the number of the ECG measurements used to derive the subject specific hysteresis and heart rate corrections were based on previous experience.

In spite of these limitations, the study shows clearly that the correction for QT/RR hysteresis is of importance when investigating QTc changes by drugs that have such a fast action that ECGs cannot be obtained only during episodes of stable heart rates. Since the technology also improves the stability of QTc data obtained in the thorough QT/QTc studies investigated drugs without fast actions, it can only be recommended that the correction for QT/RR hysteresis is incorporated in all clinical QT investigations irrespective of their nature, especially is the assessment is made without the need for a separate exercise test. The results of the study also confirmed previous observations that gadobutrol administration is not related to any torsadogenic risk.

APPENDIX

In the present study, the following method was used to obtain the λ parameter for each participant. The method was a generalization of a previously published approach.¹⁷

The QT interval measurements obtained in the superimposed median beats of the ECG segments extracted from the exercise test recordings were projected into individual complexes of the segments by using a measurement projection algorithm similar to that previously described by Berger et al.²⁶ In this way, a sequence $\{QT_i\}_{i=1}^N$ of QT interval measurements was obtained together with a matrix $\{\{RR_j^{(i)}\}_{j=1}^{M(i)}\}_{i=1}^N$ of RR interval history of each QT measurement (QT_i measurement being preceded by RR interval durations of $\{RR_j^{(i)}\}_{j=1}^{M(i)}$, where $M(i) \geq m$ for all i . (Based on previous experience, we used $m = 250$.) While all RR values were appropriately validated, the sequence of QT

contained gaps in valid data due to nonmeasurable complexes. Let $\mathfrak{S} \subseteq [1 \dots N]$ denote the set of indexes i for which the QT_i interval measurement is valid.

The so-called direct search algorithm^{27–29} was used to find sequences $\{\{\vartheta_k^{(p)}\}_{k=1}^m\}_{p=A}^L$ such that for all p and k , $0 \leq \vartheta_k^{(p)} \leq 1$ and $\sum_{k=1}^m \vartheta_k^{(p)} = 1$ for all p . For the definition of these sequences, 12 different regression formulae were considered:

- (a) $\Phi_A(\alpha, \beta, \Theta_i) = \alpha + \beta \times \Theta_i + \varepsilon_i^{(A)}$
- (b) $\Phi_B(\alpha, \beta, \Theta_i) = \alpha + \beta / \Theta_i + \varepsilon_i^{(B)}$
- (c) $\Phi_C(\alpha, \beta, \Theta_i) = e^\alpha \times \Theta_i^\beta \times e^{\varepsilon_i^{(C)}}$
- (d) $\Phi_D(\alpha, \beta, \Theta_i) = \alpha + \beta \times \ln(\Theta_i) + \varepsilon_i^{(D)}$
- (e) $\Phi_E(\alpha, \beta, \Theta_i) = \ln(\alpha + \beta \times \Theta_i + \varepsilon_i^{(E)})$
- (f) $\Phi_F(\alpha, \beta, \Theta_i) = \alpha + \beta \times e^{-\Theta_i} + \varepsilon_i^{(F)}$
- (g) $\Phi_G(\alpha, \beta, \Theta_i) = \alpha + \beta \times \arctan(\Theta_i) + \varepsilon_i^{(G)}$
- (h) $\Phi_H(\alpha, \beta, \Theta_i) = \alpha + \beta \times \tanh(\Theta_i) + \varepsilon_i^{(H)}$
- (i) $\Phi_I(\alpha, \beta, \Theta_i) = \alpha + \beta \times \operatorname{arcsinh}(\Theta_i) + \varepsilon_i^{(I)}$
- (j) $\Phi_J(\alpha, \beta, \Theta_i) = \alpha + \beta \times \operatorname{arccosh}(\Theta_i + 1) + \varepsilon_i^{(J)}$
- (k) $\Phi_K(\alpha, \beta, \Theta_i) = \alpha + \beta \times \sqrt{(\Theta_i) + \varepsilon_i^{(K)}}$
- (l) $\Phi_L(\alpha, \beta, \Theta_i) = \alpha + \beta \times \sqrt[3]{(\Theta_i) + \varepsilon_i^{(L)}}$

and the sequences $\{\{\vartheta_k^{(p)}\}_{k=1}^m\}_{p=A}^L$ were optimized such that the regression models

$$\left\{ QT_i = \Phi_X(\alpha^{(X)}, \beta^{(X)}, \left[\sum_{k=1}^m (RR_k^{(i)} \times \vartheta_k^{(X)}) \right] \right\}_{i \in \mathfrak{S}}$$

led to the smallest regression residuals $\{\sum_{i \in \mathfrak{S}} (\varepsilon_i^{(p)})^2\}_{p=A}^L$ among all possible sequences $\{\{\vartheta_k^{(p)}\}_{k=1}^m\}_{p=A}^L$.

For each $p = A, \dots, L$, the sequence of values $\{\varpi_{(p)}(w) = \sum_{k=1}^w \vartheta_k^{(p)}\}_{w=1}^m$ was linear-regression approximated by a parametric sequence $\{\hat{\varpi}_{(p)}(w) = \sum_{k=1}^w \frac{1 - e^{\lambda(p) \frac{w}{m}}}{1 - e^{\lambda(p)}}\}_{w=1}^m$ thus defining the value of $\lambda(p)$. Finally, the median value λ was obtained from all $\lambda(p)$ for $p = A, \dots, L$.

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