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The Use of In Vitro Dissolution Test for Assessment of Bioequivalence of Oral Solid Preparations in Japanese Guidelines

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The Ministry of Health, Labor and Welfare for Japan revised the Guidelines for Bioequivalence Studies of Generic Products and the new guidelines have been in force since 1997. Two of the important changes to the guidelines are the inclusion of acceptance criteria for the assessment of bioequivalence and the description of a dissolution test that has multiple uses.

It is recommended that a cross-over design be used for bioequivalence studies. In principle, healthy adult volunteers participate in such studies. The number of participants should be sufficient to assess bioequivalence and further study may be necessary if the number of subjects is found to be inadequate. Usually, a single dose unit is administered, in the fasting state, with 100-200 ml water, although the drug can be administered after food intake if there are good reasons to do so. A single-dose study is standard, but a multiple dose study can be done, if appropriate.

The area under the drug concentration-time curve (AUC) and maximum drug concentration reached (Cmax) are used for the assessment of bioequivalence. The trapezoidal rule is used to estimate the AUC from the observational data, from which

Cmax is also obtained. The 90% confidence intervals for the differences between the average logarithmic values of AUC and Cmax for the test and reference products should be within the acceptance range of log (0.8) to log (1.25).

The main study procedure and acceptance criteria are the same as those of the WHO guidelines. However, the Japanese guidelines use in vitro dissolution testing for multiple purposes, although consensus regarding the application of dissolution testing for the assessment of bioequivalence of oral solid products has not been reached worldwide. Therefore, I want to explain the concepts underlying the application of dissolution testing.

If the dissolution process is the rate-determining step for the in vivo bioavailability of oral solid products and if the in vitro dissolution rate values correlate with the in vivo parameters, then we will be able to use dissolution testing for assessing bioequivalence. However, many results tell us clearly that the in vitro dissolution rates of products from multiple sources do not always correlate with their bioavailabilities. Therefore, we conclude that we can not use in vitro dissolution tests in place of human study to assess the bioequivalence of oral solid products from multiple sources. Consequently, very large numbers of subjects, for example, more than 40 or 50, will be required to assess the bioequivalence of drugs that show very marked inter-and intra-individual variations in bioavailability.

We have studied the relationship between the bioavailabilities and dissolution rates of nalidixic acid tablets from 5 manufacturers. Unfortunately, we could not find a set of in vitro dissolution test conditions that yielded a significant correlation between the dissolution rate and bioavailability. The dissolution rates were determined under various

test conditions and we tried the oscillating, beaker, rotating flask, rotating basket and paddle test methods. We varied the volume and pH of the test fluid and the rotation speed. Tablets, A, B, D and E showed similar pharmaceutical characteristics and their relative dissolution rates were the same even when they were tested under quite different conditions, whereas the relative position of tablet C in this series changed according to the test method used. There was no significant correlation between the dissolution rate and either Cmax, the time to reach the maximum drug concentration (tmax) or the AUC, but the rank orders of Cmax, tmax and AUC among tablets A, B, D and E corresponded exactly to the rank order of their in vitro dissolution rates. Only tablet C failed to show this relationship. Based on these results we are fairly confident that we will be able to use the dissolution test to estimate the rank order of bioavailability of products whenever a constant rank order of the dissolution rates is observed with different test methods and various test conditions. The pharmaceutical characteristics of a group of products are likely to be very similar when their relative dissolution rates are the same under various test conditions.

Based on these data and considerations, the Japanese guidelines for bioequivalence studies state that the in vitro dissolution test can be used for the assessment of bioequivalence in the case of a drug with highly variable bioavailability. When a bioequivalence study involving not less than a total of 20 subjects has been done and the difference between the average logarithmic AUC and Cmax values of the two products has been shown to be between log (0.9) and log (1.1), but, unfortunately, the 90% confidence intervals are not within the acceptance range, the guidelines state that the

test product can be accepted as bioequivalent to the reference product if the dissolution rates of the two products are equivalent under all the test conditions specified.

The methods used for dissolution testing are as follows. The number of runs is 12 and the test time is less than 2 hours when the pH of the test fluid is 1.2 and 6 hours with other test fluids. The JP paddle method with 900 ml test fluid at 37°C is used and the dissolution rates are determined under multiple conditions and compared. For products containing acidic drugs, the dissolution rates in the test fluid at pH 1.2, an appropriate pH between 5.5 and 6.5 and between 6.8 and 7.5 and in water with the paddle rotating at 50 rpm are determined. The dissolution rate is also determined at 100 rpm using the test fluid that yielded the slowest dissolution rate under the above conditions.

The acceptance criteria for equivalence of dissolution profiles are as follows. When the average amount of the reference product dissolved reaches 85% within 15 minutes, the average amount of the test product dissolved should also reach 85% within 15 minutes. When the average amount of the reference product dissolved is 85% between15 and 30 minutes, the average amounts of the test product dissolved should not deviate by more than 15% from those of the reference product at two time points when the average amounts of the reference product dissolved are around 60% and 85%. The lag time for dissolution can be corrected and for the correction, the difference between the average lag times of the test and reference products should be less than 10 minutes. When the average amount of the reference product dissolved is 85% between 30 minutes and 6 hours, the average amounts of the test product dissolved should not deviate by more than 15% from those of the reference product at two time points when the average amounts of the reference product dissolved are around 40% and 85%. When the average amount of

reference product dissolved does not reach 85% within 6 hours, the average amounts of the test product dissolved should not deviate by more than 15% from that of the reference product at 6 hours and at the time point when the average amount of the reference product dissolved is approximately half that at 6 hours.

The Japanese guidelines state that the difference between the dissolution rates of two products can be ignored when the average amounts of both products dissolved reach 85% within 15 minutes at 50 rpm. Therefore, the Japanese guidelines judge that the bioavailability of such drugs will be determined by the permeability of the gastrointestinal (GI) tract or gastric emptying, not by the dissolution rates of the products. However, the critical value of the time difference is controversial.

We studied the critical time difference for dissolution that will enable discrimination of products with bioavailabilities determined by GI tract permeability or dissolution. We used acetaminophen as a model drug and prepared three solid preparations, one granule formulation and two tablets, that showed different dissolution rates. The granules (G) dissolved rapidly, 85% dissolved within 15 minutes at 50 rpm, 85% of tablet A dissolved between 15 and 30 minutes, whereas, it took between 30 and 60 minutes for 85% of table B to dissolve. These preparations were administered to 21 healthy male subjects under fasting conditions according to a cross-over design. We found no significant differences among the AUC values, but the Cmax values differed significantly. The average difference between the Cmax values of the granules and tablet A was only 8%, but that between tablets A and B was 20%. The Cmax values for the granules and tablet A, 85% of both of which dissolved within 30 minutes, were almost

identical. These and other results suggest that the critical time for discriminating the determining step for bioavailability may now be extended from 15 to 30 minutes.

The new Japanese guidelines state that the difference between lag times for dissolution can be ignored when it is less than 10 minutes. We studied the relationship between the difference in lag times observed with in vitro dissolution testing and the difference in lag times or absorption rates in humans in vivo. We prepared three different solid preparations, one capsule and two tablets, containing the same dose of acetaminophen. The lag times for dissolution were 0.45 minutes for the capsule, 8 minutes for tablet A and 17 minutes for tablet B. These preparations were administered to 21 healthy male subjects under fasting conditions according to a cross-over design. There were no significant differences among the AUC and Cmax values for these preparations, but we detected significant differences among the tmax values. The lag time for in vivo absorption seems to be extended by around 20 to 30 minutes when the lag time for in vitro dissolution observed at 50 rpm increases by 10 minutes. From these results, it seems reasonable to correct for in vitro lag times of 10 minutes or more when comparing dissolution profiles. After repeating these studies, we will be able to get more information on the relationship between differences in the dissolution rate and bioavailability. When we have such information, we should know whether we will be able to use in vitro dissolution tests more extensively to provide additional data for assessing the bioequivalence of oral solid products.