Digoxin—The Regulatory Viewpoint

As discussed in the editorial by Levy and Gibaldi, bioavailability* studies have made an important contribution to the assurance of quality and equivalency of different formulations of a given drug. Digoxin serves as a good illustrative example of the regulatory as well as the scientific problems which arise when differences in bioavailability are identified. Just prior to the initial bioavailability studies reported by Lindenbaum et al., the Food and Drug Administration (FDA) had identified digoxin tablets whose content uniformity failed to meet United States Pharmacopeia (USP) standards. As noted in the preceding editorial, this problem had brought digoxin under intensive scrutiny by FDA’s National Center for Drug Analysis (NCDA). At one point, samples from 20 of 32 firms failed content uniformity tests, and 32 out of 69 batches on the market had to be recalled because of content uniformity variability. The bioavailability experiments were repeated using tablets from lots that showed acceptable tablet content uniformity and this confirmed that a bioavailability problem existed with certain products. Shaw, Binnion, Bertler, and Jouneila, among others, have also reported the presence of a bioavailability problem with digoxin.

Before turning to the problems involved in setting regulatory standards for digoxin bioavailability, let us consider the potential impact of regulatory action. The information available suggests that most currently marketed tablets of digoxin are 50% to 75% as bioavailable as a solution of digoxin with only a few being about 10% as bioavailable (table 1). The recommended doses of digoxin which are discussed in package inserts, texts, and on teaching rounds and, more importantly, the experience of practicing physicians, are based on tablets with this 50-75% range of bioavailability. As Levy and Gibaldi point out, biopharmaceutists feel that it is possible and therapeutically desirable to create tablets as bioavailable as the digoxin solution. Based on extensive discussions with clinicians, including cardiologists, FDA finds only limited support for this view. The preponderance of medical opinion has been that products having maximum bioavailability should not be marketed without more knowledge about the clinical significance of the higher blood levels achieved more rapidly by such products as compared with digoxin on the market today. Medical concern has been expressed over the health hazards which might be brought about through unanticipated changes in bioavailability in a drug with a low toxic-therapeutic ratio like digoxin.

The potential for higher bioavailability may present a special problem. Based on experience with other drugs, when manufacturers are forced to reformulate because of a problem with a product, they do not just try to develop a minimally acceptable formulation but to produce the best possible product. Because of this, FDA considers it necessary to impose maximum as well as minimum dissolution standards until more information is available on the actual blood levels achieved by currently marketed products. If FDA were to impose only a minimum standard for digoxin tablets we can anticipate that manufacturers with unacceptable tablets (5-10% of the market), in reformulating might introduce new products with higher bioavailability than currently acceptable tablets. In all likelihood this would force manufacturers with currently acceptable tablets, perhaps 50-75% as bioavailable as the new formulations, to reformulate to make their tablets as bioavailable as the reformulated tablets in order to compete successfully. The effect of this would be that rather than just 5-10% of the patients taking digoxin being at risk from changes in the potency of their tablets, 90-95% of patients would be affected. Although the danger from a change in formulation would not be as great to the group on currently acceptable tablets, new recommendations for usage need to be developed based in part on an assessment of the clinical importance of peak blood levels 2-3 times as high as current tablets produced ½ to 1 hour after dosing. Although individual physicians might be capable of establishing new practices in their use of digoxin on the basis of trial and error experience, it seems more reasonable to develop the necessary

*The bioavailability of an active ingredient(s) from a drug product is defined as the rate and extent to which the ingredient(s) is absorbed and becomes available to the site of action.

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information on the basis of controlled clinical studies. Consequently the FDA proposed an upper limit on the dissolution at one hour of currently marketed digoxin tablets. This will necessitate that new formulations with significantly faster dissolution be treated as new drugs requiring clinical studies.

The problems of setting in vitro and in vivo standards are well illustrated by digoxin. The release of drug from the dosage form into solution in the gastrointestinal fluids is often the rate-limiting step in determining the rate and extent of absorption. When this is true, in vitro measurements of dissolution provide a rapid, reproducible means to study these events. For some drugs in vitro dissolution rates may be predictive of the rate or amount of absorption of the products studied. Hence, in vitro dissolution testing may be used as a monitor of differences in bioavailability of some drugs. Several methods have been advocated for dissolution testing of digoxin tablets. Two methods, for which published in vitro-in vivo correlations exist, have been used at the National Center for Drug Analysis (NCDA).

Although some batches show about the same results when tested by both methods, others show large differences. Figure 1 shows representative dissolution results obtained, in this case with water and the rotating paddle. From the two manufacturers whose multiple lots are cited, the amount of lot-to-lot variability within the same formulation can be seen. It is obvious that there are significant differences in the dissolution rates of different formulations and their dissolution rates form a continuous spectrum rather than dividing clearly into “good” and “bad” products. A pass-fail line cannot be drawn with confidence on the basis of such data.

What correlations are available from bioavailability testing? Table 1 shows the correlation of dissolution rates and peak blood levels following 0.5 mg doses of digoxin tablets from 28 lots of 11 manufacturers. These results are a composite of published and FDA in-house and contract studies done under different conditions and are not ideal for decision making, yet they are the data upon which the Agency must act if it is going to act. The data show that there is a rough correlation between in vitro dissolution rates and in vivo bioavailability studies and support further studies to attempt to develop the dissolution test as the in vitro test for lot-to-lot quality control of formulations.

What cannot always be seen from the published

in vitro-in vivo correlation is the large amount of inter- and intra-subject variability seen in patients receiving digoxin which makes the in vivo studies relatively insensitive to detecting differences between formulations as compared with in vitro dissolution testing. Levy and Gibaldi may be correct that steady state bioavailability studies will be better than single dose studies in terms of ability to discriminate but currently there are insufficient data to confirm this. Thus, the FDA has little choice but to base its decisions and regulatory actions on single dose studies at the moment.

The problem of what formulations should be the standard for bioavailability studies in human subjects and how much deviation from the standard should be allowed, or more appropriately, can be detected is also difficult. The FDA has received conflicting expert opinion unsupported by actual data on digoxin. These viewpoints are reflected in

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the following different recommendations: (1) that
an oral solution be established as the standard with
which tablet absorption should be compared;
(2) that an intravenously administered solution be
used as the standard; and (3) that a currently accep-
table tablet formulation be the standard. To
collect additional data to resolve these differences
of opinion and to increase the potential of inter-
preting results from individual bioavailability
studies, the FDA is proposing a triple crossover
experiment with 0.5 mg of USP digoxin in solution
and 0.5 mg of a single well-characterized lot of
digoxin tablets to be run with each formulation
tested.

While these studies are being conducted by the
manufacturers to validate the bioavailability of
their formulation, the FDA will require that each
lot of digoxin be tested and have 55-95% dissolu-
tion by the method recently adopted by the USP in its
6th Interim Revision.6

The NCDA will also do dissolution tests on lots
analyzed by the manufacturers to determine the
reliability of their testing procedures. The NCDA
will then certify the manufacturers’ dissolution test-
ing procedures based on reproducing their results.

The NCDA recently tested 31 lots of digoxin
obtained in a sampling program and found that 10
lots representing nine manufacturers failed the
USP dissolution test. These manufacturers will be
allowed to reformulate to comply with the dissolu-
tion test. However, the FDA recommends that they
reformulate their products to give a dissolution be-	ween 70 and 90% by the other dissolution tests
as well as the USP method. This recommendation
is based on the assumption that a narrower range
of dissolution will lead to greater product uniform-
ity, and the expectation that as bioavailability
data are collected and correlated with the dissolu-
tion test results, the acceptable range will be nar-
rowed. To assist the manufacturers in developing
formulations which meet this recommendation, the
NCDA will do dissolution testing on all new formu-

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<td><strong>Available Data Correlating Dissolution and Peak Blood Levels</strong></td>
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Abbreviations: B.L. = blood level in ng/ml; Invest = investigator; Dissolution = % of digoxin released in one hour by paddle-water method.
lations by the USP procedure and the paddle-water method. This will aid in defining subtle differences between formulations.

Once a company has a formulation that has passed the dissolution test, it will be required to monitor each lot by dissolution testing. No company will be allowed to market a revised formulation without first establishing the bioavailability of the new formulation if its dissolution rate is outside the 55-95% range in one hour by the USP dissolution test.

Although this approach has delayed action by the FDA while it developed in its own laboratories and through contract research sufficient data to take the above action, it is hoped and anticipated that through this approach the period of increased differences between formulations can be controlled and the ultimate uniformity of digoxin products can be established with the least risk to patients currently on digoxin. The approach will require reformulation by companies with products that have dissolution rates below 55%. It is anticipated that when sufficient bioavailability data are available on different formulations, the question of what the standard dissolution test method should be can be settled and more rigorous dissolution standards can be set on the basis of additional data correlating in vitro with in vivo testing.

As pointed out in the editorial by the New York Heart Association, the FDA solicits the cooperation and understanding of the professional societies, cardiologists and other health professionals in trying to achieve the transition to optimum digoxin therapy with as little risk as possible to patients.

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Jerome P. Skelly
Arthur W. Steers

References
9. United States Pharmacopeia, 18th revision, Sixth Interim Announcement, Nov. 15, 1973
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