BIOAVAILABILITY EDITORIALS

Bioavailability of Drugs
Focus on Digoxin

During the last ten years there have appeared a considerable number of well-designed and controlled studies which demonstrate that the rate and/or extent of absorption of a drug may differ among products from different manufacturers. These reports have dealt with tetracycline, oxytetracycline, chloramphenicol, ampicillin, diphenylhydantoin, and digoxin, among many others. It is now well known that this difference in absorbability, commonly referred to as bioavailability, is a significant problem requiring the attention of governmental agencies, physicians, pharmacists and pharmaceutical scientists. A recently published book summarizes the proceedings of the Conference on Bioavailability of Drugs which was held in 1971 at the National Academy of Sciences of the United States. This conference served to summarize the many studies of drug bioavailability carried out up to 1971 and provided an insight to the many pharmaceutical formulation factors which can modify bioavailability. These include particle size and shape, crystal form, the kind and quantity of lubricant, disintegrant, coloring agent or other formulation adjuvants, and other variables. While much is now known about the pharmaceutical formulation factors which influence drug bioavailability and the mechanisms which account for differences in the bioavailability of different products of the same drug or different lots of the same product, much less is known about the therapeutic implications of such differences and about the design of proper standards and tests to assure adequate bioavailability of drug products. A significant contribution to the development of bioavailability test methods are the "Guidelines for Biopharmaceutical Studies in Man," published recently by the Academy of Pharmaceutical Sciences.

Some of the clinical implications of incomplete bioavailability, methods of bioavailability testing, and approaches to the design of bioavailability standards can be discussed by focusing on digoxin. Sufficiently sensitive methods for determining the very low concentrations of this drug in the plasma have been developed and are readily available. The pharmacokinetics of digoxin in man are reasonably well (though not completely) defined. The usual therapeutic plasma concentration range of digoxin has been determined and it has also been established that most patients with digoxin intoxications have plasma concentrations which are about twice the average therapeutic concentration. The available information indicates, for example, that a 50 percent change in the steady-state plasma concentration of digoxin may bring a patient into either the subtherapeutic or toxic concentration range. The need to assure the adequate bioavailability of digoxin products is therefore readily apparent.

About two years ago, an unexplained association of unusually large maintenance doses of digoxin and low serum digoxin concentrations in several patients prompted Lindenbaum and co-workers to determine serum digoxin levels over a 5-hour period after oral administration of single doses of four different digoxin products to normal volunteers. This study suggested that there may be pronounced differences in the bioavailability of different commercially available digoxin tablet products. This was subsequently substantiated in two pharmacokinetically rigorous investigations. Huffman and Azarnoff found that the digoxin tablet product most widely used in the United States (Lanoxin) was only 75 percent absorbed on the average in normal volunteers relative to an oral solution of this drug. Wagner and associates reported similar results and found also that the bioavailability of another digoxin tablet preparation on the American
market was only half that of Lanoxin. We recently have been made aware that some other digoxin products may show an even lower bioavailability (reference 18 and personal communication from M. Weintraub). There have also been observations of significant differences between lots from a single manufacturer16 and it has been demonstrated that an unannounced change in pharmaceutical formulation also resulted in pronounced changes in the bioavailability of digoxin tablets.19, 20 It is quite clear that these bioavailability problems can be ascribed primarily to inadequate dissolution of digoxin in gastrointestinal fluids since it has been possible to demonstrate in vitro that relatively well absorbed preparations dissolve much more rapidly than poorly absorbed ones.17, 21

At this time there is no evidence that any commercially available digoxin tablet preparation on the American market is fully bioavailable as compared to an orally administered solution. It might be argued that incomplete bioavailability is not objectionable as long as the extent of bioavailability of any one product is consistent and known to the prescriber so that he can adjust the dosage accordingly. Unfortunately, this reasoning is incorrect. Incomplete bioavailability is associated with increased variability in absorption relative to preparations which are completely or almost completely absorbed. This is apparent in comparing the relative standard errors of serum digoxin concentrations obtained after administration of the drug in solution or in tablets to normal subjects.7 It is even more strikingly apparent in studies on the effect of gastrointestinal motility on digoxin absorption. In patients on maintenance digoxin tablet therapy, concomitant administration of the anticholinergic drug propantheline caused as much as a three-fold increase in serum digoxin concentrations while metoclopramide, which increases gastrointestinal transit rate, produced a marked decrease in digoxin concentrations.22 Significantly, propantheline had no effect on digoxin concentrations when digoxin was administered in solution; it only affected the absorption of digoxin from relatively poorly absorbed tablets. It is therefore essential that drugs with a relatively unfavorable therapeutic index, such as digoxin, be administered in a dosage form which affords maximum bioavailability (i.e., similar to that of a solution) because changes in gastrointestinal physiology due to disease or concomitant drug therapy may have pronounced effects on the bioavailability of an incompletely absorbed product.

It is necessary to take into consideration one other potential source of variability and that is the lack of content uniformity of digoxin in some tablet preparations.23 Fortunately, this problem now appears to be under reasonable control in the United States because the Food and Drug Administration has initiated an intensive analytical monitoring program to assure that individual tablets do not differ significantly in content of digoxin. Several recalls of digoxin tablets have been required by the Food and Drug Administration due to excessive tablet-to-tablet variation of content. On the other hand, it is curious and regrettable that the Food and Drug Administration has not removed even the most poorly absorbed digoxin tablet product from the market, at the time that this is being written, even though the agency is fully aware of the problem.

One is now faced with the task of developing adequate means of assuring the bioavailability of digoxin tablets. This will require, first of all, the reformulation of existing products, then the adoption of adequate methods to determine and monitor bioavailability, and finally the development of suitable in vitro tests to serve as an in-house control to minimize lot-to-lot variations. The reformulation of digoxin tablets and the development of appropriate in vitro dissolution tests should present no insurmountable problems, given the present sophistication in the pharmaceutical sciences, but a difficult decision will have to be made with respect to the best method of assessing bioavailability. Basically, the question is whether this assessment should be carried out in normal volunteers or in patients who require digoxin therapy. While it has been traditional to use normal volunteers and to carry out single dose bioavailability studies, we believe that it is preferable to assess the bioavailability of digoxin under steady-state conditions in patients on digoxin therapy. The basis of our position in this matter evolves directly from the question for which one seeks the answer: how well will patients who require digoxin absorb the drug from a particular product?

The regular monitoring of digoxin concentrations in the plasma is now considered to be in the patients’ best interest and has become part of therapeutic management in certain institutions which have the requisite analytical facilities. The use of steady-state plasma concentrations for bioavailability monitoring has been publicly advocated since 1971 and presents certain pharmacokinetic advantages.24 The usefulness of this
method for assessing digoxin bioavailability has been demonstrated.\textsuperscript{26} It involves the determination of plasma digoxin concentrations on several days during the regular administration of a suitable standard product such as digoxin elixir in patients who have been receiving this product for some time (for at least ten days), followed by a change to an equal dose of the product to be tested while plasma concentration monitoring is continued. Plasma concentrations will decrease slowly if the test product is less completely absorbed than the standard. Use of the test product is discontinued as soon as such a trend is evident and before the digoxin concentrations fall below the therapeutic range. In patients with normal renal function it should even be possible to monitor digoxin bioavailability at the steady state by determining the daily output of this drug in the urine, i.e., in a noninvasive manner. The use of urinary excretion data has the additional advantage of overcoming problems in the timing of blood samples which may be a source of difficulties and misinterpretation of plasma digoxin concentration data obtained during chronic drug administration.\textsuperscript{26}

The digoxin bioavailability problem is immediate and serious. At the same time the requisites for the solution of this problem are readily available: sensitive analytical methods, adequate knowledge of the pharmacokinetics and of the relationship between plasma concentration of digoxin and its pharmacologic effect, and technology for the formulation and production of tablets with acceptable bioavailability characteristics. In moving toward the solution of the digoxin bioavailability problem, government, industry, and medical and pharmaceutical scientists can set an example for overcoming similar problems with other drugs.

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