DRUG QUALITY CONTROL: PROBLEM WITH DIGOXIN[1]

In a recent monitoring program on digoxin tablets, the FDA's National Center for Drug Analysis reported that 47% of the batches investigated did not comply with the requirements of the USP monograph, chiefly because of failure in the content uniformity test. In one of the worst examples, NCDA found digoxin tablets containing twice the declared quantity of active ingredients. The same bottle contained tablets with 60-70% of the declared quantity. The manufacturers agreed to recall the violative lots. A follow-up program on digoxin tablets is underway, and the Bureau of Drugs is monitoring production to assure content uniformity of individual tablets.

On the basis of the digoxin findings, and other studies of diverse pharmaceutical products containing high potency drug substances in relatively low concentrations, FDA has concluded that direct tests for content uniformity are essential. Testing of bulk formulation material has proved unreliable as a measure of uniform content in individual dosage units. When such procedure is used, it is still possible for many of the tablets punched from the formulation mass to fall far outside permissible potency limits.

The significance of this finding to the prescribing physician is obvious: If a previously well-digitalized patient displays signs of under or over-digitalization, the problem may be with the drug rather than with the patient. Certainly, this possibility should be borne in mind when such signs appear.

The Food and Drug Administration is working to eliminate the problem of variable potency and its Bureau of Drugs has undertaken extensive investigations. In establishing the National Center for Drug Analysis, the Bureau has significantly expanded its capacity for gauging the quality of drug control in general. As a result of the Center's marked success in developing automated methods of analysis and applying them to individual units of dosage forms, NCDA is now able to focus attention on problem situations involving deviations from content uniformity requirements.

[1] Adapted from a paper delivered at the Mid-Year Meeting of the National Association of Pharmaceutical Manufacturers, February 14, 1971, at Washington, D.C., by Daniel Banes, Ph.D., Director, Office of Pharmaceutical Research and Testing, Bureau of Drugs, FDA.

ISONIAZID: LABELING CHANGES

In 1970 following the discovery of active tuberculosis in several employees on Capitol Hill in Washington, D.C., a large number of individual employees were placed on isoniazid for prophylactic purposes. Several developed jaundice. There were two deaths from hepatitis. This precipitated new consideration of the hepatic side effects of isoniazid. An intensive review of isoniazid followed. Involved in this review were the National Center for Disease Control, the FDA's Advisory Committee on Anti-Infective Agents, the American Thoracic Society, and the National Tuberculosis and Respiratory Disease Association.

Available evidence could not support a conclusion that the two Capitol Hill deaths were caused by isoniazid. However, it did become evident that reports of hypersensitivity reactions such as hepatic dysfunction were more frequent than had been generally recognized.

As a result of the review of isoniazid, changes have been made in the package insert. These changes have the support of the agencies identified above.

FDA urges your attention to the new "Warnings" statement in the package insert. It is evident that careful and periodic monitoring of the patient is advisable to permit earlier identification of the signs and symptoms of liver toxicity. At the first sign of hypersensitivity, including hepatitis, all drugs should be stopped. If isoniazid is reinstituted, it should be in small and gradually increasing doses to determine whether the manifestations are drug-induced. Preventive treatment for tuberculosis should be deferred in individuals with acute hepatic disease.

The package insert should be consulted for further guidance. A Guest Editorial, "Isoniazid and the Liver," follows.