as well as differences in the two standard deviations, and since the means themselves are tested for equality in the ANOVA, the 75/75 Rule also might be said to place the test product in double jeopardy.

The stress placed previously (1) on a "well-defined reference standard which has reproducible pharmacokinetic properties in terms of absorption and clearance" or "an oral solution" makes us ask just where the criterion of acceptable reproducibility of a reference standard is set down?

(1) B. E. Cabana, *J. Pharm. Sci.*, **72**, 98 (1983).
(2) J. D. Haynes, *ibid*, **70**, 673 (1981).
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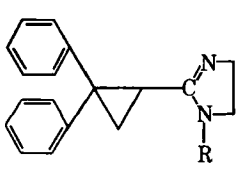
Radioimmunoassay for the New Antiarrhythmic Agent Cibenzoline in Human Plasma

Keyphrases □ Cibenzoline—new antiarrhythmic agent, radioimmunoassay in human plasma □ Antiarrhythmic agent—cibenzoline, radioimmunoassay in human plasma □ Radioimmunoassay—cibenzoline, a new antiarrhythmic agent, human plasma

To the Editor:

Cibenzoline [*dl*-4,5-dihydro-2-(2,2-diphenylcyclopropyl)-1H-imidazole] (I), a new oral antiarrhythmic agent with a novel chemical structure, is presently undergoing clinical evaluation. The present report describes the development and characteristics of a radioimmunoassay for cibenzoline which permits its quantitation directly in human plasma.

To obtain antibodies to cibenzoline, an immunogen was first prepared by covalently coupling the N_1-acetic acid derivative of cibenzoline[1] (II), as a hapten, to bovine serum albumin using a mixed anhydride procedure (1). Rabbits were immunized with the resulting conjugate, and the antiserum with the highest titer of antibodies of cibenzoline was used.



I: R = —H
II: R = CH_2CO_2H

The radioligand used for the assay was [^{3}H]cibenzoline with a specific activity of 10.8 Ci/m*M*[2]. Prior to use, radiochemical purity was established by TLC on silica gel using ethyl acetate–methanol–ammonia (80:15:5) as the solvent system.

The radioimmunoassay was carried out in 12 × 75-mm disposable glass tubes using 0.1 *M* phosphate buffered saline (pH 7.4) containing 0.1% gelatin and 0.1% sodium azide as the assay buffer. Plasma samples (0.02–0.1 ml) containing standard or unknown concentrations of cibenzoline were mixed with 0.2 ml of [^{3}H]cibenzoline in buffer (10,000 cpm) followed by 0.2 ml of diluted antiserum (1:600), and the mixture was incubated at 4° for 30 min. Then, 1 ml of a stirred suspension of a polymer-bound second antibody (goat anti-rabbit IgG)[3] was added and the tube contents were vortexed briefly and allowed to stand at 4° for 1 hr. Following centrifugation at 2000 rpm for 10 min, each supernatant was aspirated off, the pellet suspended in 0.4 ml of 1 *M* acetic acid, and mixed with 3 ml of scintillation fluid[4]. The tube was capped and radioassayed directly in a liquid scintillation counter[5] modified as described previously (2). A calibration curve was generated using a four-parameter logistic curve-fitting program for a desktop calculator[6] (3).

The logit-log calibration curve for cibenzoline was linear from 4 to 200 ng/ml using a 0.1-ml sample of plasma. Such sensitivity is adequate for the quantitation of cibenzoline following administration of therapeutic doses of the drug. The intra- and interassay coefficients of variation (n = 6) did not exceed 6.5 and 10%, respectively, over a range of 38–219 ng/ml of cibenzoline in a selection of random clinical samples. Although the antiserum was found to cross-react almost 100% with the 4,5-dehydro derivative of cibenzoline, a known metabolite of the drug in the dog[7], the specificity of the radioimmunoassay for the analysis of human plasma samples was evaluated by comparison with a specific electron-capture GLC method which was developed and utilized at another research institution[8]. For 57 clinical samples analyzed by both procedures (radioimmunoassay = y), the correlation coefficient, regression line slope, and y-intercept were 0.98, 0.93, and 16, respectively, over a range of 12–287 ng/ml. Although the slope and intercept were significantly different than 1 and 0, only 4 of the 57 highly correlated (r = 0.98) observed data points lay outside the 95% confidence limits of the fitted regression line, which indicates that the radioimmunoassay is in reasonable agreement with a specific chromatographic procedure for the quantitation of cibenzoline. It has been shown by high-performance liquid chromatography (4) that only trace amounts of the 4,5-dehydro metabolite of cibenzoline are present in human plasma, and the metabolite is separated from the parent drug in the electron-capture GLC assay.

In subjects who had received 65 mg of the drug three times a day for 6 days, the peak plasma concentrations at steady-state were ~300 ng/ml of cibenzoline.

A simple radioimmunoassay procedure with adequate sensitivity and specificity was developed for the quanti-

[1] The hapten was prepared from cibenzoline by alkylation with ethyl chloroacetate in ethanol followed by base hydrolysis and crystallized from isopropanol–ether as a partial hydrate, mp 202–204°. The MS and NMR spectra were compatible with the proposed structure.
[2] Prepared by Chemical Research Division, Hoffmann-La Roche Inc.
[3] Roche Diagnostics, Nutley, NJ 07110.
[4] Aquasol, New England Nuclear Corp., Boston, MA 02118.
[5] Packard Tri-Carb model 3255.
[6] TI-59, Texas Instruments, Lubbock, TX 79408.
[7] Data on file, Hoffmann-La Roche Inc.
[8] Personal communication, Laboratoires UPSA, Rueil Malmaison, France.

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tation of cibenzoline in clinical plasma samples and shown to be specific for the drug in human plasma.

(1) B. F. Erlanger, F. Borek, S. M. Beiser, and S. Lieberman, *J. Biol. Chem.*, **234**, 1090 (1959).

(2) R. Dixon and E. Cohen, *Clin. Chem.*, **22**, 1746 (1976).

(3) M. L. Jaffe, P. J. Munson, and D. Rodbard, "Four Parameter Logistic Curve-Fitting Program for the TI-59 Calculator," National Institute of Child Health, National Institutes of Health, Bethesda, MD 20014.

(4) M. R. Hackman, T. L. Lee, and M. Brooks, *J. Chromatogr.*, in press.

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BOOKS

Pharmaceutics and Pharmacy Practice. Edited by GILBERT S. BANKER and ROBERT K. CHALMERS. Lippincott, East Washington Square, Philadelphia, PA 19105. 1981, 421 pp. 18 × 25 cm. Price $27.50.

Pharmaceutics and Pharmacy Practice, for the most part, is well written, with each chapter containing much good information, with 23 authors contributing some interesting chapters.

The preface states that the book represents a new approach by interrelating pharmaceutical and clinical pharmacy knowledge about drugs and their delivery systems; however, it contains a standard chapter on physical–chemical principles and another on basic biopharmaceutics. Since the later chapters on drug-delivery systems (oral, topical, parenteral, *etc.*) relate appropriate physical–chemical and biopharmaceutics to their specific subjects, there would be no loss if the physical–chemical chapter were deleted. The chapter on biopharmaceutics could be shortened, except for the portion relative to proper interpretation of blood level curves and evaluation of bioequivalence, which could have been expanded.

The chapter, "Drug Development and Quality Evaluation," would benefit from an expansion of the discussion of selection of multisource drug products and a condensation of federal drug regulatory matters. Similarly, the chapter, "Patient Factors that Influence Dosage Form Selection," should have been edited to remove dosage, patient acceptance (also covered in "Oral Drug-Delivery Systems") and biopharmaceutic matters, while the chapter, on patient education could have been expanded in order to more closely approach the interrelation of knowledge. The style of the chapter on literature resources appears to be better suited to a work book and is repetitious.

The last six chapters are gems. Each one contains relevant anatomy and physiology, routes of drug delivery, drug-delivery systems (dosage forms), and therapeutic considerations. They also contain appropriate physical–chemical considerations and biopharmaceutical aspects. In this manner are covered the drug-delivery systems for oral, parenteral, topical (skin), topical (eye, ear, nose), inhalation, and rectal, vaginal, and urethral administration. A few considerations of extemporaneous preparation of delivery systems are to be found in all of these chapters.

While the book is described as being intended for adult professionals, the preface refers to the book's predecessor as being *Prescription Pharmacy*, which would indicate that one concern would be the dispensing function (the pharmacy practice of the title). Noticeably lacking is any information about processing the prescription, maintenance of prescription files or records, legal aspects of dispensing controlled substances, hospital pharmacy, or the use of computers in pharmacy. While the chapter on parenteral drug-delivery systems contains good material on TPN and electrolyte therapy, no mention is made of aseptic methods appropriate for making intravenous admixtures, *etc.* Thus, the book appears to be written from the aspect of pharmaceutical technology rather than pharmacy practice.

Although the editors were only partly successful in their attempt to interrelate pharmaceutical and clinical pharmacy to pharmacy practice, this book contains much excellent information presented in a highly readable manner.

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Analytical Profiles of Drug Substances, Vol. 10. Edited by KLAUS FLOREY, *et al.* Academic, 111 Fifth Ave., New York, NY 10003. 1981. 735 pp. 14 × 23 cm.

Analytical Profiles of Drug Substances, Vol. 10 continues the successful series of complete monographs for important drug substances. This series is compiled under the auspices of the Pharmaceutical Analysis and Control Section of the Academy of Pharmaceutical Sciences. Volume 10 contains monographs on aminosalicylic acid, azathioprine, benzyl benzoate, clindamycin hydrochloride, codeine phosphate, colchicine, cyanocobalamin, emetine hydrochloride, glibenclamide, heroin, hydrochlorothiazide, ketoprofen, methylphenidate hydrochloride, nabilone, natamycin, oxytocin, penicillamine, probenecid, salbutamol, succinylcholine chloride, and trioxsalen. There also are *errata* for cefamandole nafate, fluphenazine decanoate, gentamicin sulfate, and nadolol.

The typical monograph contains the following information: First, there is an initial description including nomenclature, formula, and other physical descriptions followed by a physical properties section which usually covers crystal properties, melting point characteristics, solubility, and spectral properties including reproductions of IR, UV, NMR, and mass spectra. Usually there is a discussion on the drug's synthesis or biosynthesis followed by the drug's metabolism. The monographs usually conclude with a literature review of different methods for analyzing the drug.

There is no question that this series fills a need. The surprising fact is, that after nine previous volumes, the editors still have not developed a standard format for the monographs. Here are some examples of inconsistencies. The Chemical Abstracts Service (CAS) Registry Number is given in 11 of the 21 monographs. When present, it may be in Section 1.1 1, 1.23, 1.2.3, 2.1, 1.2.1, 1.12, or 1.14. Wiswesser Line Notation is present in five of the monographs, and the elemental composition will be found in only eight monographs. Six of the monographs open with one or more introductory paragraphs containing information on the drug's history and use. When this is present, the nomenclature material found in Section 1 now goes into Section 2.

Section 5.5, when present, can be UV spectrometry, proton magnetic resonance spectrometry, radioassay, phosphorimetry, colorimetry, and other unrelated topics. Putting it another way: suppose an analytical chemist wishes to examine the applicability of high-pressure liquid chromatography for a drug analysis whose monograph has been published in this series. Where does he or she look? Answer: Somewhere near the end of the monograph, but be careful, because the material on chromatography may be divided between methodology, analysis of dosage forms, and analysis from biological fluids.

Make no mistake, *Analytical Profiles of Drug Substances* belongs in the personal libraries of drug analysts. Teachers in the field should purchase it as well as school, university, and company libraries. In addition, the publishers and editors should be encouraged to investigate a student rate for graduate students in pharmaceutical analysis. At the same time, some active editing would correct glaring inconsistencies and deficiencies and make the *Analytical Profiles* series reflect the care and consistency expected of the profession and the Academy.

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