Liquid Chromatographic Analysis of Cimetidine with Procainamide as Internal Standard

Keyphrases □ Cimetidine—HPLC analysis in plasma and urine □ Liquid chromatography—analysis of cimetidine in plasma and urine

To the Editor:

We recently reported in this journal a simple and sensitive liquid chromatographic assay for cimetidine in plasma and urine (1). Chromatographic separation was performed on a radially compressed column[1], which allowed much faster and more efficient chromatography than previously described assays (1). However, since burimamide (the internal standard) is no longer manufactured, this has rendered our assay inapplicable by other investigators. We have therefore examined the chromatography of a wide variety of other compounds, including many other H_2-antagonist analogues, and found procainamide to be the most suitable alternative internal standard to burimamide. This results in minimal modification of our originally published assay.

In the analysis of plasma, procainamide hydrochloride[2] (20 μg/mL, 100 μL, in a 0.09% sodium metabisulfite solution), sodium hydroxide (2 M, 0.5 mL), and dichloromethane (20 mL) were added to 1.0 mL of plasma in a 30-mL glass tube. In the analysis of urine, procainamide hydrochloride[2] (1 mg/mL, 25 μL, in a 0.09% sodium metabisulfite solution), sodium hydroxide (2 M, 100 μL), and dichloromethane (5 mL) were added to 250 μL of urine in a 30-mL glass tube. Thereafter, the method of extraction and reconstitution of both plasma and urine samples was identical to that previously reported (1). The mobile phase, radial compression column[1], chromatographic conditions, and instrumentation were as reported previously (1). Procainamide (2.6-min retention) and cimetidine (3.8-min retention) were completely resolved. Cimetidine sulfoxide (1.5-min retention), the major metabolite of cimetidine (2), did not interfere with the assay. The analytical recoveries of cimetidine and procainamide were 60 and 59%, respectively. The coefficient of variation for within-day assays of plasma cimetidine levels was 1.8% at 1000 ng/mL (n = 6); for urine it was 0.53% at 50 μg/mL (n = 6). The coefficient of variation of between-day assays of plasma cimetidine levels over 4 weeks was 5.2% at 901 ng/mL (n = 7); for urine over 4 weeks the value was 5.4% at 51.0 μg/mL (n = 5).

The assay was applied to the measurement of plasma and urine samples obtained from a patient who underwent intravenous and oral cimetidine therapy in pharmacokinetic studies according to the protocol reported previously (1). The same samples were also analyzed for cimetidine by our original liquid chromatographic method (1) with burimamide as internal standard. There was good correlation between the two methods (r = 0.991), and the cimetidine levels did not significantly differ (paired t test, $p \geq 0.20$, df = 20) between the assays.

Thus, with a change in internal standard from burimamide to procainamide, this method can still be applied to the assay of cimetidine in biological fluids, without a major change in methodology.

[1] Rad Pak A and RCM-100, Waters Associates, Milford, Mass.
[2] Sigma Chemical Company, St. Louis, Mo.

(1) G. W. Mihaly, S. Cockbain, D. B. Jones, R. G. Hanson, and R. A. Smallwood, *J. Pharm. Sci.*, **71**, 590 (1982).
(2) D. C. Taylor, P. R. Creswell, and D. C. Bartlett, *Drug Metab. Dispos.*, **6**, 21 (1978).

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BOOKS

A Textbook of Pharmaceutical Analysis, 3rd Ed. By KENNETH A. CONNORS. Wiley-Interscience, 605 Third Avenue, New York, NY 10016. 1982. 664 pp. 15 × 23 cm. Price $55.00.

This book is the latest revision in what is by now a classic text in pharmaceutical analysis for the undergraduate pharmacy curriculum. The first and second editions were issued in 1967 and 1975. The field of "pharmaceutical analysis" has undergone enormous changes over the 15 years this text has been used. Whether the sample be raw materials, dosage forms, or biological fluids, the methodology is more selective, more precise, and more accurate. As a reflection of modern developments, the latest edition includes a chapter on immunoassay and a substantially expanded chapter on liquid chromatography. Both of these subjects scarcely existed in 1967 (especially with respect to determination of pharmaceuticals), and now they are prominent in virtually every issue of this journal.

As was the case with previous editions, this book meets its objectives very well. I especially like Connor's focus on chemical reactions and his liberal use of examples, practice problems, and laboratory experiments. He is at his best when describing the interface between fundamental chemistry and instrumentation. It is delightful to see organic reaction mechanisms and stereochemistry taken into consideration. So many analytical chemistry texts are stuck on inorganic things and gadgets and thus miss the needs of many students.

The only fault I find with this book is that it is too much material for the undergraduate level and not quite enough to be useful as a graduate text for junior researchers. It just misses these audiences by dropping in between, a problem that can be solved by selective assignments and supplementary material. Overall, a job well done!

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