in individuals (29). Therefore, individuals taking amino acid–iron complexes should be made aware that such products do not have value as protein supplements or replace the need for dietary protein. In addition, depending on the quantity and essentiality of the amino acids ingested from the supplement, protein metabolism may be adversely affected.

A consensus has been reached that amino acids considered to be essential are isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine for children and adults. Histidine is an essential amino acid for infants, but it is not considered essential for children or adults (30). It is important to note that the amino acids that appear to increase the absorption of iron are not considered to be essential amino acids. Nitrogen balance is maintained by an adequate diet of protein and not by an iron supplement containing one or two amino acids in very low quantities (29, 30). Likewise, increasing the dosage of the amino acid by taking more tablets of an amino acid–iron preparation could cause iron toxicity.

REFERENCES

(1) A. Albert, *Biochem J.*, **47**, 531 (1950).

(2) A. Albert, *Biochem J.*, **50**, 690 (1952).

(3) A. Albert, *Biochem J.*, **76**, 621 (1960).

(4) D. Kroe, T. D. Kinney, N. Kaufman, and J. V. Klavins, *Blood*, **21**, 546 (1963).

(5) D. Kroe, T. D. Kinney, N. Kaufman, and J. V. Klavins, *Am. J. Physiol.*, **211**, 414 (1966).

(6) D. Van Campen and E. Gross, *J. Nutr.*, **99**, 69 (1969).

(7) D. Van Campen, *J. Nutr.*, **102**, 165 (1972).

(8) D. Van Campen, *J. Nutr.*, **103**, 139 (1973).

(9) W. Forth and W. Rummel, in "International Encyclopedia of Pharmacology and Therapeutics," Vol. II, Pergamon, Great Britain, 1975, p. 599.

(10) M. C. Linder and H. N. Munro, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **36**, 2015 (1977).

(11) H. J. Helbeck and P. Saltman, *Biochim. Biophys. Acta*, **135**, 979 (1967).

(12) E. R. Monsen and J. D. Cook, *Am. J. Clin Nutr.*, **29**, 442 (1976).

(13) T. Peters, L. Apt, and J. F. Ross, *Gastroenterology*, **61**, 315 (1971).

(14) H. C. Heinrich, H. Bartel, E. E. Gabbe, G. Kugler, and K. H. Oppitz, *Arzneim-Forsch.*, **22**, 1091 (1972).

(15) E. R. Monsen and J. F. Page, *J. Agric. Food Chem.* **126**, 223 (1978).

(16) F. E. Viteri, R. Garcia-Ibanez, and B. Torum, *Am. J. Clin. Nutr.*, **31**, 961 (1978).

(17) H. C. Heinrich, in "Clinical Symposium on Iron Deficiency," L. Hallbreg, H. G. Harwerth, and A. Vannotti, Eds., Academic, New York, N.Y., 1970, p. 213.

(18) F. H. Meyers, E. Jawetz, and A. Goldfien, "Medical Pharmacology," 6th ed., Lange Medical Publications, New York, N.Y., 1975, p. 457.

(19) A. D. A. Miski and F. H. Kretzner, *J. Nutr.* **107**, 24 (1977).

(20) A. L. Lehninger, "Biochemistry," 2nd ed., Worth Publishers, New York, N.Y., 1975, p. 488.

(21) V. Herbert, in "The Pharmacological Basis of Therapeutics," 4th ed., L. S. Goodman and A. Gilman, Eds., MacMillan, New York, N.Y., 1970, p. 1398.

(22) M. Layrisse, J. D. Cook, C. Martines-Torres, M. Roche, J. A. Kuhn, and C. A. Finch, *Blood*, **33**, 430 (1969).

(23) O. Greengard, A. Sentenan, and N. Mendelsohn, *Biochem. Biophys.*, **90**,406 (1964).

(24) C. Martines-Torres and M. Layrisse, *Am. J. Clin. Nutr.*, **24**, 531 (1971).

(25) L. Hallburg and L. Rossander, *Am. J. Clin. Nutr.* **35**, 502 (1982).

(26) R. B. Chodos, I. F. Ross, L. Apt, M. Pollycore, and I. Hallett, *J. Clin. Invest.*, **36**, 314 (1957).

(27) P. C. Elwood, D. Newton, J. D. Eakins, and P. A. Brown, *Am. J. Clin. Nutr.*, **21**, 1162 (1968).

(28) L. Jansky and J. S. Hart, *Can. J. Physiol. Pharmacol.*, **46**, 653 (1968).

(29) M. I. Irwin, *J. Nutr.* **101**, 385 (1970).

(30) M. I. Irwin and D. M. Hegsted, *J. Nutr.* **101**, 539 (1971).

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Evaluation of High-Performance Liquid Chromatography and Gas Chromatography for Quantitation of Dextromethorphan Hydrobromide in Cough–Cold Syrup Preparations

V. GIBBS ˣ **and Z. ZAIDI**

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Abstract □ A rapid and sensitive high-performance liquid chromatographic (HPLC) procedure is described for the analysis of the antitussive dextromethorphan hydrobromide in several cough–cold syrup preparations and compared with a gas chromatographic (GC) procedure. In the HPLC procedure, the active ingredient is analyzed as the hydrobromide salt by dilution in the mobile phase and separation on a reverse-phase cyano column. In the GC method, the active ingredient is analyzed as the free base, in which an aqueous solution of the antitussive is made alkaline and extracted with dichloromethane before injection onto the GC column. Excellent resolution of the antitussive agent was obtained by both systems; however, the HPLC assay is preferred for routine analysis (*RSD* 1%), as compared with the GC assay (*RSD* 4%).

Keyphrases □ Dextromethorphan hydrobromide—HPLC, GC □ Antitussive agents—dextromethorphan hydrobromide, HPLC, GC □ Formulations—cough–cold syrup, analyses by HPLC and GC

Dextromethorphan hydrobromide [(+)-3-methoxy-17 methyl-9α,13α,14α-morphinan hydrobromide monohydrate (I)] is commonly used an an antitussive agent in many commercial cough–cold syrup preparations. There are several clinically active compounds classified as morphinans. All have the drawbacks of morphine: its dependence liability and respiratory-depressant characteristics (1). However, the side effects of some morphinans are not as severe as those of morphine. As a result, dextromethorphan hydrobromide has gained wide acceptance as a nonaddictive antitussive agent because it is nearly devoid of any analgesic activity (2).

Dextromethorphan hydrobromide has been separated by

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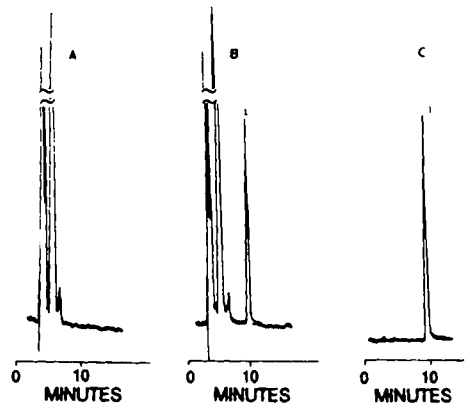

Figure 1—*Chromatograms of a typical HPLC run of placebo (A), sample syrup (B), and standard (C). Key: (1) dextromethorphan hydrobromide.*

use of various chromatographic procedures when present alone (3) and in combination (4–10) with other active ingredients. Foremost in this category is high-performance liquid chromatography (HPLC), employing either ion-pair (6, 9) or buffer systems (8, 10). Since cough–cold syrups usually contain a combination of many active ingredients, the ability to analyze a full range of amine ingredients in cough–cold syrups by a single assay has been emphasized by most of these methods, as opposed to one single active ingredient in a range of multicomponent cough–cold syrup preparations. In our laboratory, the application of several of these HPLC procedures to various marketed cough–cold syrups containing dextromethorphan hydrobromide was unsuccessful in separating the active ingredient each time. In addition, excessive retention times and peak tailing were also experienced in some cases. To our knowledge, we are unaware of any reported chromatographic procedure which is broadly applicable to the analysis of dextromethorphan hydrobromide in a variety of cough–cold syrups containing several active ingredients, as well as various excipients, dyes, and/or sugar bases. Reported gas chromatographic (GC) methods usually involve an extraction step and prove to be better at resolving dextromethorphan hydrobromide from various excipients present in cough–cold syrups. However, sufficient recovery data have not been reported (4, 5).

The purpose of this study was to develop a rapid and sensitive method for analyzing dextromethorphan hydrobromide in several cough–cold syrup preparations, regardless of formula subtleties and, subsequently, to compare the efficiency of GC and HPLC for completing this task. In this paper, the application of HPLC and GC to several different cough syrups containing dextromethorphan hydrobromide as an active ingredient is described.

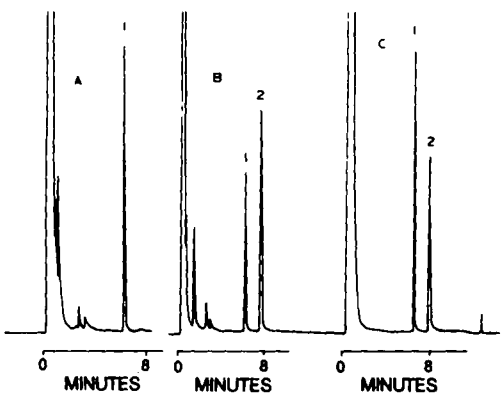

Figure 2—*Chromatograms of a typical GC run for placebo with internal standard (A), spike placebo (B), and standard (C). Key: (1) O-methoxyphenyl benzoate; (2) dextromethorphan hydrobromide.*

Table I—Recoveries by High-Performance Liquid Chromatography

Formulation I[a]			Formulation II[b]		
Amount Added, mg	Amount Found, mg	Recovery, %	Amount Added, mg	Amount Found, mg	Recovery, %
1.01	1.02	100.9	1.01	1.01	100.0
3.03	3.00	99.0	3.03	3.04	100.3
5.04	5.06	100.4	5.04	4.99	99.0
			7.24	7.29	100.7
			8.28	8.36	100.9
			10.35	10.37	100.2
			15.52	15.63	100.7
Mean		100.1			100.2
RSD, %		0.98			0.64

[a] 10 mL of placebo was spiked with the added amount of standard; I, contained no other active ingredients. [b] 5 mL of placebo was spiked with the added amount of standard; II, contained 12.5 mg of phenylpropanolamine hydrochloride and 20% alcohol.

EXPERIMENTAL SECTION

Chemicals and Reagents—Methanol, acetonitrile, and dichloromethane were distilled in glass[1] (HPLC grade). Perchloric acid (60% v/v), potassium nitrate, and anhydrous sodium sulfate were either ACS or analytical reagent grade[2].

High-Performance Liquid Chromatography—The liquid chromatograph[3] was fitted with an automatic injector[4] and a variable-wavelength UV detector[5] set at 280 nm. A microparticulate cyano column[6] (25 cm × 4.6 mm i.d.), containing 5-μm particles, was used.

Chromatographic Conditions—The mobile phase was 0.05 M potassium nitrate in acetonitrile–water (25:75), with the pH adjusted to 3.0 ± 0.1 with 60% v/v perchloric acid; the flow rate was 1.5 mL/min. The mobile phase was filtered[7] and deaerated before use. The inlet pressure was approximately 2900 psi. Detector sensitivity was 0.2 AUFS, the chart speed was 0.25 cm/min, and the injection volume was 10 μL.

Standard Preparation—Three working standard solutions were prepared by diluting 3, 5, and 8 mL of dextromethorphan hydrobromide[8] stock standard solution (1 mg/mL), respectively, to 100 mL with the mobile phase in volumetric flasks. Solutions were mixed and filtered[7].

Sample Preparation—Samples (2–10 mL, depending on label claim) were accurately transferred to 100-mL volumetric flasks and diluted to volume with the mobile phase. Solutions were mixed and filtered.

Gas Chromatography—The gas chromatograph[9] was a dual column modular system equipped with 1–10-mV recorder[10].

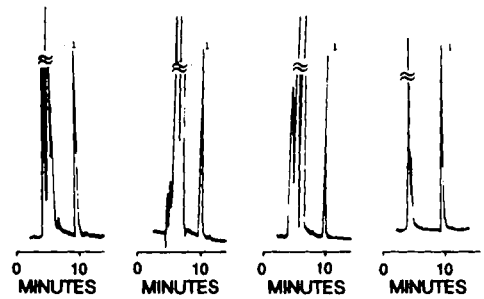

Figure 3—*HPLC analysis of four different commercial cough–cold syrups containing dextromethorphan hydrobromide. Key: (1) dextromethorphan hydrobromide.*

[1] MCB Manufacturing Chemists, Cincinnati, Ohio.
[2] J. T. Baker Chemical Co., Phillipsburg, N.J.
[3] Model SP 8000 equipped with a printer/plotter; Spectra Physics, Santa Clara, Calif.
[4] Auto Injector model 725; Micromeritics Instruments, Norcross, Ga.
[5] Spectroflow Monitor SF 770; Schoeffel Instruments, Westwood, N.J.
[6] IBM Instruments, Danbury, Conn.
[7] Hydrophilic type HV filter, 0.45-μm pore size; Millipore Corp., Bedford, Mass.
[8] USP reference standard or house-calibrated standard.
[9] Aerograph model 3700 TC-FID gas chromatograph; Varian Instruments Associates, Walnut Creek, Calif.
[10] Omniscribe Linear Recorder; Houston Instruments, Austin, Tex.

Table II—Recoveries by Gas Chromatography

Formulation II[a]			Formulation III[a]		
Amount Added, mg	Amount Found, mg	Recovery, %	Amount Added, mg	Amount Found, mg	Recovery, %
3.05	3.32	108.8	3.59	3.62	100.8
5.08	5.18	101.9	5.59	5.80	103.7
5.19	5.15	99.32	8.39	9.05	107.8
7.11	7.72	104.8	10.68	10.92	102.2
15.48	16.13	104.2	11.68	12.66	108.4
			16.28	16.95	104.1
Mean		103.8			104.5
RSD, %		3.4			2.9

[a] 5 mL of placebo was spiked with the added amount of standard; II, contained 12.5 mg of phenylpropanolamine hydrochloride and 20% alcohol; III, contained 20% alcohol.

Chromatographic Conditions—A glass column[11] (~1.8 m × 2 mm i.d.) packed with 3% OV-17 on Chromasorb Q[12] (100–120 mesh) was used. The column temperature was maintained at 110°C for 2 min and programmed to 230°C for 4 min at 30°C/min. The flow rate of the helium carrier gas was 25 mL/min, with an inlet pressure of 30 psi. The injector port temperature was 220°C. The detector temperature was 260°C, with a hydrogen flow rate of 30 mL/min and an air flow rate of 300 mL/min. Detector sensitivity was 10^{-9} with a chart speed of ~0.5 cm/min. The temperature program was initiated with each 5-μL injection[13]. The column was allowed to condition overnight at 240°C before use.

Standard Preparations—Standard solutions of dextromethorphan hydrobromide were prepared by accurately weighing 1–15 mg of dextromethorphan hydrobromide standard into a 60-mL separatory funnel containing 25 mL of 0.1 M NaOH. The separatory funnel was stoppered and shaken gently to dissolve the solid, and the free base was extracted with three 15-mL portions of dichloromethane. After each addition of the organic solvent, the separatory funnel was stoppered and shaken vigorously for 15 min. The organic layer was transferred to a 50-mL volumetric flask *via* a funnel containing 200 mg of sodium sulfate supported by glass wool. Two milliliters of a 2.5-mg/mL solution of *O*-methoxyphenyl benzoate[14] in chloroform was added as internal standard to each flask before diluting to volume with dichloromethane.

Sample Preparations—Samples (5–10 mL, depending on label claim) were accurately transferred to 60-mL separatory funnels and extracted in the same manner as described above for the standards.

Assay Procedure and Quantitation—Under the chromatographic conditions described for HPLC and GC, injections of the sample and standard solutions were made. Results were calculated from the linear regression of the three standards, relating peak height ratios (standard-internal standard) and concentration.

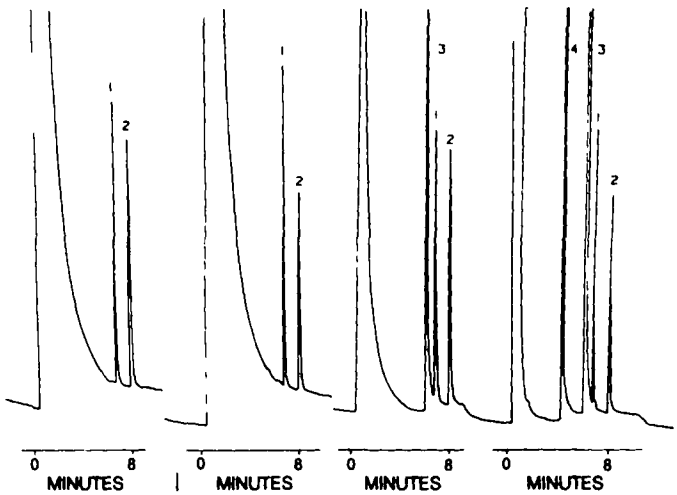

Figure 4—*Chromatograms of a typical GC run of four different commercial cough-cold syrups. Key: (1) O-methoxyphenyl benzoate; (2) dextromethorphan hydrobromide; (3) guaifenesin; (4) pseudoephredine hydrochloride.*

[11] Supelco, Bellefonte, Pa.
[12] Applied Science Laboratories, College Park, Pa.
[13] Microliter syringe, 701N; Hamilton Co., Reno, Nev.
[14] Pfaltz and Bauer Chemical Co., Stamford, Conn.

Table III—Comparative Analysis of Dextromethorphan Hydrobromide by HPLC and GC

	Precision Data				
	HPLC[a]			GC[a]	
Sample	I	II	III	I	III
1	2.46	5.17	15.52	2.57	16.73
2	2.43	5.19	15.50	2.61	16.26
3	2.42	5.18	15.57	2.65	16.61
4	2.38	5.26	15.52	2.49	14.99
5	2.47	5.29	15.59	2.66	16.52
6	2.42	5.31	15.43	2.61	16.87
7	2.42	5.22	15.59	2.77	16.77
8	2.46	5.27	15.43	2.76	17.10
9	2.42	5.28	15.61	2.75	16.06
Mean	2.43	5.24	15.53	2.65	16.43
RSD, %	1.15	0.90	0.43	3.5	3.8

[a] Formulation I, contains no other active ingredients; formulation II, contains 12.5 mg of phenylpropanolamine hydrochloride and 20% alcohol; formulation III, contains 20% alcohol.

RESULTS AND DISCUSSION

Preliminary studies involved testing of several mobile phase compositions for effective separation of dextromethorphan hydrobromide in a cough-cold syrup base. A 25:75 ratio of acetonitrile–water was finally found to be suitable for all the products analyzed. Peak tailing was minimized by using 0.05 M potassium nitrate and adjusting to pH 3.0. Several microparticulate reverse-phase columns with octadecylsilane (C_{18}) and cyano (CN) packings were tried from various manufacturers. In the past, C_{18} columns have been widely used by other workers for the separation of amines in cough-cold syrup preparations. In our experience, these columns (30 cm × 3.9 mm i.d. of 10-μm particle size) did not give suitable separation of dextromethorphan hydrobromide in some of the products analyzed. Finally, a cyano column (5-μm particle size; 25 cm × 4.6 mm i.d.) was used and was found to be more selective for the antitussive agent and, hence, provided better separation of the active ingredient from other excipients. Since the ultimate objective was to develop a method which would work for other commercially available products as well, column selection was considered to be an important factor.

Typical chromatograms of a placebo and sample run by HPLC are shown in Fig. 1. Construction of a standard curve from injections of dextromethorphan hydrobromide standard solutions ranging from 1 to 10 mg demonstrated the linearity of the HPLC procedure. The average peak height response was 8.98 cm for a 5-mg standard solution (*RSD* 1.6%). The limit of detection was 0.005 mg/mL for a steady baseline at 280 nm. The GC procedure offered comparable detection, and the standard curve was also found to be linear for solutions ranging from 1 to 15 mg. The average peak height response was 8.56 cm for a 5-mg standard solution (*RSD* 3.5%). Chromatograms of a GC run are shown in Fig. 2.

Data generated from the recovery studies by HPLC and GC are outlined in Tables I and II, respectively. The recoveries were performed by an external standard addition method. To evaluate the precision of the two methods, multiple injections of a single lot of cough syrup were made (Table III). For each formulation under investigation, the *RSD* was <1.5% for the HPLC assay and <4.0% for the GC assay. Although the HPLC assay is an external standard method, it was believed that the addition of an internal standard would not significantly improve the precision of the assay procedure. However, if an internal standard is desired, methaphenilene hydrochloride and promethazine can be used for this purpose. The retention times are 14.0 and 20.0 min, respectively, relative to dextromethorphan hydrobromide, which has a retention time of 10.0 min.

The second phase of the study involved the evaluation of both assay pro-

Table IV—Comparative Analysis of Dextromethorphan Hydrobromide in Commercial Products

		HPLC		GC	
Product[a]	Claim, mg	Found, mg[b]	Percent Label Claim	Found, mg	Percent Label Claim
A	15	14.95	99.6	14.82	98.8
B	10	10.18	101.8	10.92	109.2
C	10	9.99	99.9	10.82	108.2
D	30	29.08	96.9	30.31	101.0

[a] A, contained 100 mg of guaifenesin/5 mL and 1.4% alcohol; B, contained 5% alcohol; C, contained 100 mg of guaifenesin and 30 mg of pseudoephedrine hydrochloride/5 mL and 2.4% alcohol; D, contained 9.5% alcohol. [b] Results are the average of duplicate determinations.

cedures (HPLC and GC) for determining dextromethorphan hydrobromide from other commercially available cough syrups. Chromatograms obtained for these products were representative of the assay procedure and gave resolution and/or separation similar to that of dextromethorphan hydrobromide in the products under investigation. Typical chromatograms are shown in Figs. 3 and 4 for HPLC and GC, respectively, and the results are compared in Table IV.

The results obtained by the GC procedure were higher for all the products analyzed and, hence, reflected the difficulty in extracting the free base with organic solvents (10). This difficulty was experienced with the standard and sample solutions as well. It is believed that the partitioning behavior (11) of the antitussive agent is the major cause for this problem rather than the complexity of the cough syrup formulations. The GC procedure involved a lengthy sample preparation and required more analysis time as compared with the HPLC procedure. Finally, the HPLC procedure gave results that were in better agreement with label claims for all the products evaluated and was a more precise assay procedure.

CONCLUSION

Although excellent resolution of the antitussive agent was obtained by both the HPLC and GC systems, further examination of the applicability of either method for routine analysis of dextromethorphan hydrobromide revealed that the HPLC procedure described is simple, rapid, and precise for the quantitation of the antitussive agent in several commercially available cough-cold syrups. The GC procedure does not seem to be the method of choice for quantitation of dextromethorphan hydrobromide in cough syrups due to the difficulty in extracting the free base and the time involved in sample preparation.

REFERENCES

(1) Alfred Burger, "Medicinal Chemistry," part II, 3rd ed., Wiley-Interscience, New York, N.Y. 1970.

(2) R. Grewe and A. Mondon, *Chem. Ber.*, **91**, 279 (1948).

(3) E. J. Kubiak and J. W. Munson, *J. Pharm. Sci.*, **69**, 1380 (1980).

(4) J. L. Fabregas and A. Margalet, *J. Pharm. Sci.*, **64**, 1005 (1975).

(5) E. R. Kaplan and A. A. Spark, *So. African J. Sci.*, **71**, 241 (1975).

(6) G. W. Halstead, *J. Pharm. Sci.*, **71**, 1108 (1982).

(7) G. W. Schieffer and D. E. Hughes, *J. Pharm. Sci.*, **72**, 55 (1983).

(8) W. O. McSharry and I. V. E. Savage, *J. Pharm. Sci.*, **69**, 212 (1980).

(9) M. K. Chao, I. J. Holcomb, and S. A. Fusari, *J. Pharm. Sci.*, **68**, 1463 (1979).

(10) A. Menyhareth, F. P. Mahn, and J. E. Heveran, *J. Pharm. Sci.*, **63**, 431 (1974).

(11) T. Higuchi *et al.*, *Anal. Chem.*, **39**, 974 (1967).

(12) P. Mukerjee, *Anal. Chem.*, **28**, 870 (1956).

Nasal Drug Delivery System of a Quaternary Ammonium Compound: Clofilium Tosylate

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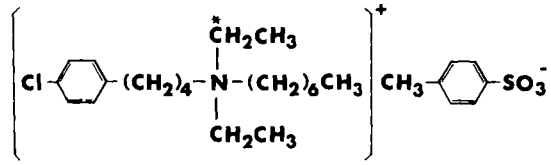
Received September 9, 1983, from the *Pharmaceutical Research Department and Pathology Division, Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN 46285.* Accepted for publication October 12, 1983.

Abstract □ The blood levels of the [^{14}C]clofilium ion in rats after various routes of administration of clofilium tosylate were compared. The results indicate that the blood levels after nasal administration were not statistically different from levels after intravenous administration ($p > 0.05$). Administration by the oral route resulted in considerably lower blood levels. Nasal administration of clofilium tosylate appeared to be superior to oral administration. Histological examinations of nasal mucosa were conducted. At the lower concentration, mild necrosis was observed, and large areas of mucosa were unaffected. However, necrosis of large areas of mucosa occurred after exposure to the higher concentration. Levels of radioactivity in heart, liver, lung, and kidney tissue, as a function of time, were also studied. Unlike the blood levels after nasal administration, the levels of radioactivity were persistent in heart tissue. The data suggest that the [^{14}C]clofilium ion and/or metabolite concentrate in the heart and that blood levels of radioactivity may not be an accurate index of cardiac levels or biological response.

Keyphrases □ Clofilium tosylate—nasal drug delivery □ Drug delivery systems—clofilium tosylate, nasal administration

Clofilium tosylate, [4-(*p*-chlorophenyl)butyl]diethylheptylammonium tosylate, is a newly synthesized quaternary ammonium compound that has been shown to selectively increase refractoriness of cardiac tissue in dogs and humans (1-3). It is known that oral administration of quaternary ammonium compounds results in low and varied blood levels (4). Predictably, the oral absorption of clofilium tosylate in rats was poor (5). A total of 0.35% of the dose was excreted in the urine and 79% was excreted in the feces within 72 h after oral administration. All tissues had extremely low levels of radioactivity and low rates of absorption after oral administration of clofilium tosylate. The pharmacokinetics and bioavailabilities of quaternary ammonium compounds given by various routes have been studied previously (4-7). However, nasal administration of a quaternary ammonium compound has not yet been evaluated. It was the object of this study to report the results on the nasal absorption of clofilium tosylate in rats. The tissue disposition of radioactivity after nasal administration of [^{14}C]clofilium tosylate is also reported.



EXPERIMENTAL SECTION

Synthesis of [^{14}C]Clofilium Tosylate—[^{14}C]Clofilium tosylate was prepared in this laboratory by Dr. F. J. Marshall. *N*-[^{14}C]Acetyl-*N*-heptyl-(4-chlorophenyl)butylamine was prepared as follows: 104.4 mg (1.33 mmol) of [^{14}C]acetyl chloride was introduced by vacuum transfer into a flask containing 804.8 mg (2.86 mmol) of 4-(4-chlorophenyl)butylamine in 13 mL of dry toluene. The mixture was then stirred for 3 h and warmed gently for 1 h in a stoppered flask. The solution was washed with 10 mL of a 1 M HCl-water-saturated sodium chloride solution and then dried with magnesium sulfate and the organic phase was evaporated to dryness under reduced pressure. The resulting material was dissolved in chloroform and purified by preparative TLC (ethyl acetate, silica gel[1]). A total of 277 mg (64% yield) of the amide was obtained. This material was reduced to the tertiary amine as follows. With cooling in ice water, a solution of 277 mg (0.855 mmol) of the aforementioned

[1] 60-F254; E. Merck, Darmstadt, Federal Republic of Germany.

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