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Stability of meperidine in an implantable infusion pump using capillary gas chromatography–mass spectrometry and a deuterated internal standard

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Abstract

A capillary gas chromatographic–mass spectrometric (GC–MS) method is described for the analysis of meperidine using 3,3,5,5-[$^2H_4$]-meperidine as an internal standard. Chromatography was performed on a (5% phenyl) methylpolysiloxane column (30 m × 0.32 mm I.D., 0.25 μm film thickness) operated at 195°C; helium carrier gas-50 cm s^{-1}, $t_R = 2.3$ min. Ionization was by electron impact (EI) and detection by selected ion monitoring of the molecular ions. The method provided high response linearity (mean $r = 0.9982$) and precision ($< 6.5\%$ C.V.). Application of this method to a pilot study of aqueous meperidine · HCl (10 mg ml^{-1}) stability in a surgically implantable infusion pump at 37°C for 90 days revealed no demonstrable drug degradation. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Meperidine (Demerol®, Fig. 1) is a phenylpiperidine type synthetic opioid analgesic used in the management of moderate to severe pain. The pharmacologic effects of meperidine are similar to those of morphine, although meperidine generally produces less constipation and urinary retention.

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Furthermore, some patients experience less nausea and vomiting with meperidine. Long-term oral or systemic meperidine administration may result in the accumulation of the hepatically formed metabolite normeperidine, especially in patients with renal dysfunction. This metabolite has been implicated in central nervous system (CNS) toxicity manifested as myoclonus, agitation, delirium, and seizures [1]. Central neuroaxial (intrathecal or epidural) administration of meperidine, however, allows for both a reduction in normeperidine formation by eliminating presystemic metabolism and a reduction in the total daily dose of meperidine by increasing the CNS bioavailability.

Continuous administration of morphine using a surgically implanted infusion pump which incorporates a drug delivery catheter routed to an intrathecal or epidural site has proven effective in controlling chronic malignant and non-malignant pain while minimizing systemic toxicities, tolerance, and other complications [2–7]. A recent clinical report extends the use of this implanted pump to meperidine in a patient who could not tolerate morphine or similar analgesics [8]. However, the stability of aqueous meperidine · HCl in such a drug delivery device residing at body temperature over a prolonged period, and while exposed to the potentially reactive (catalytic) interior surface of the pump, has not been established. This is of special concern because the meperidine molecule contains an ester, a functional group particularly prone to hydrolytic degradation. Accordingly, in the following study analytical methodology was developed to establish the compatibility of this drug under these conditions.

Previously reported methods for meperidine determinations have utilized packed column gas chromatography (GC) with flame ionization detection (FID) incorporating either no internal standard [9,10], or standardized with benzphetamine [11], *N*-methylnorlidocaine [12], 2-

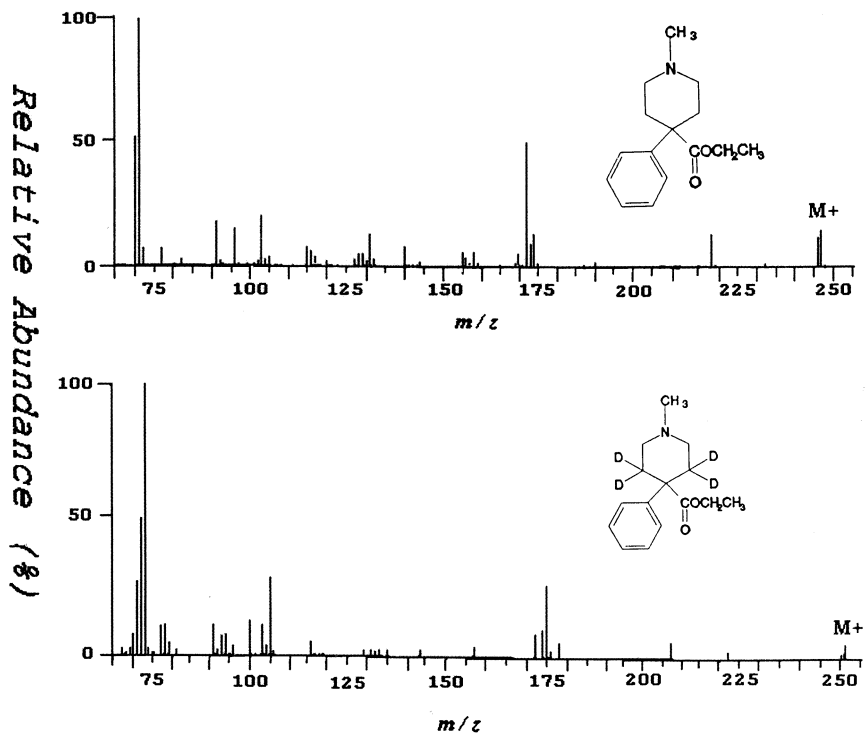

Fig. 1. Structure and EI–MS of meperidine (above) and [$^2H_4$]-meperidine (below). The molecular ion (M +) of each was selected for monitoring by GC–MS.

ethyl-5-methyl-3,3-diphenyl-L-pyrolline [13], lidocaine [14,15], or mepivacaine [16]. In addition, a capillary GC–FID method has been reported in which eicosane was incorporated as an external standard [17]. Meperidine has also been quantitated using packed column GC coupled to either an electron capture detector (ECD) where the butyl ester homolog of meperidine served as the internal standard [18–20], or a nitrogen–phosphorus detector (NPD) using *N*-ethylnormeperidine as the internal standard [21]. Packed column GC methods for meperidine determinations which benefit from the molecular specificity of mass spectrometry (MS) in the selected ion monitoring (SIM) mode have also been reported. Among these methods, lignocaine [22] and phencyclidine [23] have served as internal standards. But more ideally, deuterated isotopologs of meperidine have also seen application in this capacity. Their very similar physicochemical properties to that of the analyte allow for inherently superior analytical control. Thus, 3,3,5,5-[$^2H_4$]-piperidine labeled [24], [$^2H_5$]-ethyl labeled [25], [$^2H_5$]-labeled (positions undesignated) [26] or [$^2H_{10}$]-ethyl phenyl labeled [27,28] meperidine have all served this function with packed column GC.

The present study reports on the development of the first capillary GC–MS method for meperidine quantitation. This method was then applied to a pilot investigation of the drug stability issue described above. As with the plasma meperidine GC–MS method of Lindberg et al. [24], samples were standardized with 3,3,5,5-[$^2H_4$]-meperidine and electron impact (EI) ionization was used, but rather than employing a packed GC column, the current method for the infusate determinations offers the well documented performance advantages of capillary GC, a chromatographic system especially appropriate for interfacing with MS [29].

2. Experimental

2.1. Chemicals

Ampules (0.5 ml) of aqueous meperidine · HCl (50 mg ml^{-1}; Demerol® HCl; batch no. M050NP) were obtained from Sanofi Winthrop Pharmaceuticals (New York). Sodium chloride (0.9%) for injection (USP) was obtained from Baxter Healthcare (Deerfield, IL). 2,2,6,6-[$^2H_4$]-methanolic meperidine (0.1 mg ml^{-1}) and meperidine (1 mg ml^{-1} used for calibrator samples) were obtained from Radian International (Austin, TX). Acetonitrile was from Mallinckrodt (Paris, KY). Ethanol was from Pharmaco Products (Brookfield, CT). The infusion pump (diameter: 87 mm, thickness: 28 mm) was produced by Infusaid (Pfizer; Norwood, MA).

2.2. Sample preparation

The infusion pump was charged with 10 mg ml^{-1} meperidine · HCl diluted from the ampule concentration using isotonic saline. This was placed in an oven maintained at 37°C for 90 days. A sample (20 μl) was withdrawn from the septum equipped pump at the following times thereafter: 0.5, 5, 15, 30, 60, and 90 days. After a final sample collection, these were stored for 6 months at −30°C until analysis. Then they were diluted with ethanol (150 μl) and aliquots (10 μl) transferred to one dram screw cap vials containing [$^2H_4$]-meperidine (10 μg) each. The solutions were blown to dryness under nitrogen, then reconstituted with acetonitrile (50–100 μl) just prior to GC. These were analyzed in parallel with a set of calibration standards: 0, 2, 4, 6, 8, 10, and 12 g meperidine (calculated as HCl salt) with [$^2H_4$] meperidine (10 μg calculated as HCl salt) added to each.

2.3. Instrumental analysis

All analyses utilized a Finnigan Model 9610 GC and a model 4000 MS interfaced to an IBM-AT computer using a Teknivent Vector/One data system and software (St. Louis, MO). The injector was adapted to capillary bore using a 17.8 cm conversion sleeve and a reducing union (Supelco, Bellfonte, PA). The MS was calibrated with perfluorotributylamine (FC-43). Detection was by SIM with EI ionization at 60–70 eV and 280–300 μA. The electron multiplier was operated at 1500 V. The data system acquired two channels of ion

Table 1
Accuracy and precision

Meperidine added[a]	Detected[b] (μg)	*n*	C.V. (%)
0	0.20	6	2.14
2	1.86	6	6.40
4	3.82	6	3.55
6	5.98	6	6.20
8	8.18	6	2.62
10[c]	9.97	6	1.97
12	12.01	6	1.77

[a] Calculated to reflect meperidine concentrations as the HCl salt (0–12 mg ml^{-1}).

[b] Evaluated by back-calculating each individual calibration standard data point against the associated calibration plot. All *r* values > 0.9975 (mean 0.9982).

[c] Corresponds to initial concentration (see Section 2).

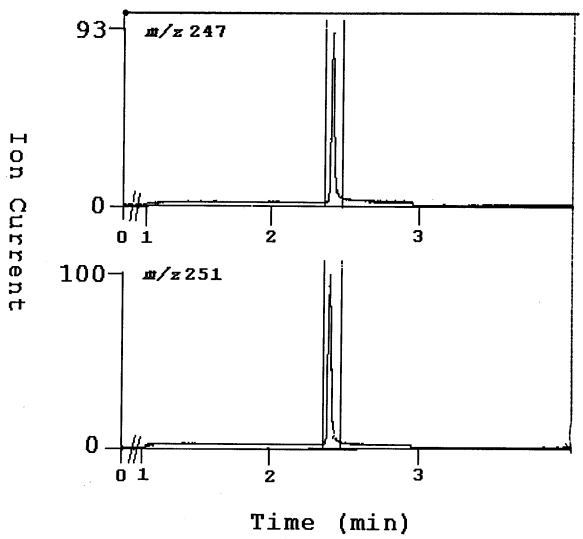

Fig. 2. Representative ion chromatograms of meperidine (above) and the internal standard deuterated meperidine (below) from a sample containing 10 μg of each. The vertical lines represent the integration boundaries used for the peak area determinations.

current: meperidine at *m/z* 247 (M+, 15% relative abundance) and the corresponding [$^2H_4$]-molecular ion at *m/z* 251. The data system scan rate was every 0.1 s with a sweep width of 0.1 a.m.u., integrating each acquisition sample for 4 ms.

A 0.5 μl Hamilton syringe was used to inject 0.1 μl by the splitless mode onto a (5% phenyl)methylpolysiloxane fused-silica column, 30 m × 0.23 mm I.D., 0.25 μm film thickness (DB-5, J&W Scientific, Folsom, CA). The filament was powered ~1.1 min after the sample injection. The GC oven was maintained isothermally at 195°C and the injection port and interface oven held at 235°C. The helium carrier gas had a linear velocity of 50 cm s^{-1}. Under these conditions, meperidine and deuterated meperidine eluted 2.25 and 2.23 min (owing to the isotope effect) after injection, respectively.

2.4. Validation and calculations

The accuracy and precision were assessed by back-calculating individual calibration standard data points using the slope and intercept of the associated standard curve from six separate runs, plotted as GC peak area ratio (meperidine/[$^2H_4$]-meperidine) versus concentration added. The concentrations of meperidine in the unknowns were then calculated from the slope and intercept of the associated calibration plot. Only single determinations were made in view of the acceptable validation data. This single determination practice is in accordance with consensus guidelines [30]. All standard concentration values were corrected to reflect the HCl form of the pharmaceutical solutions.

3. Results

A capillary GC–MS analytical method for meperidine determinations was developed and validated (Table 1). A tetradeuterated isotopolog (Fig. 1) was incorporated for analytical control. Analytical specificity for the parent drug was provided for by selective ion monitoring of the intact molecular ion; also coupled to the appropriate GC retention time for a meperidine reference standard. At the 195°C isothermal GC temperature used, rapid sample throughput was achieved (one sample/3 min; meperidine $t_R = 2.3$ min from injection) with near-Gaussian peak shape (Fig. 2). The linearity of response for the calibration plots ($n = 6$) provided a mean correlation coefficient of 0.9982; Precision was < 6.5% C.V. for all calibra-

tors (Table 1). Application of this method to the study of meperidine · HCl (10 mg ml^{-1}) stability in isotonic saline stored at 37°C, pH 5.83, in a surgically implantable infusion pump for 90 days revealed no demonstrable drug degradation (Fig. 3). The variability of the concentration values over time exhibited a C.V. (%) of 1.4. This is less than that of the precision for the calibrators. Accordingly, no evidence of meperidine hydrolytic loss was observed over the course of this study, i.e. mass balance was established without the necessity of determining concentrations of the pethidinic acid hydrolysis product. However, in that amino acids such as pethidinic acid do not elute by GC unless derivatized, this hydrolytic product would not have been detected even if decay in meperidine concentration was evident [31].

4. Discussion

The meperidine determinations made in the present study did not involve a biological matrix, nor an extraction. Hence, the analytical control function of the internal standard [$^2H_4$]-meperidine was primarily limited to any potential variability in injection volumes, column efficiency, and MS performance. However, if a modification of this capillary GC–MS method were to be adapted for bioanalyses involving pH adjustment and extraction, the [$^2H_4$]-meperidine would provide added value relative to many other reported meperidine internal standards. Meperidine is subject to temperature dependent acid and base catalyzed ester hydrolysis [32], in addition to enzymatic hydrolysis [33,34]; so with the possible exception of the closely related *N*-ethylnormeperidine [21], all

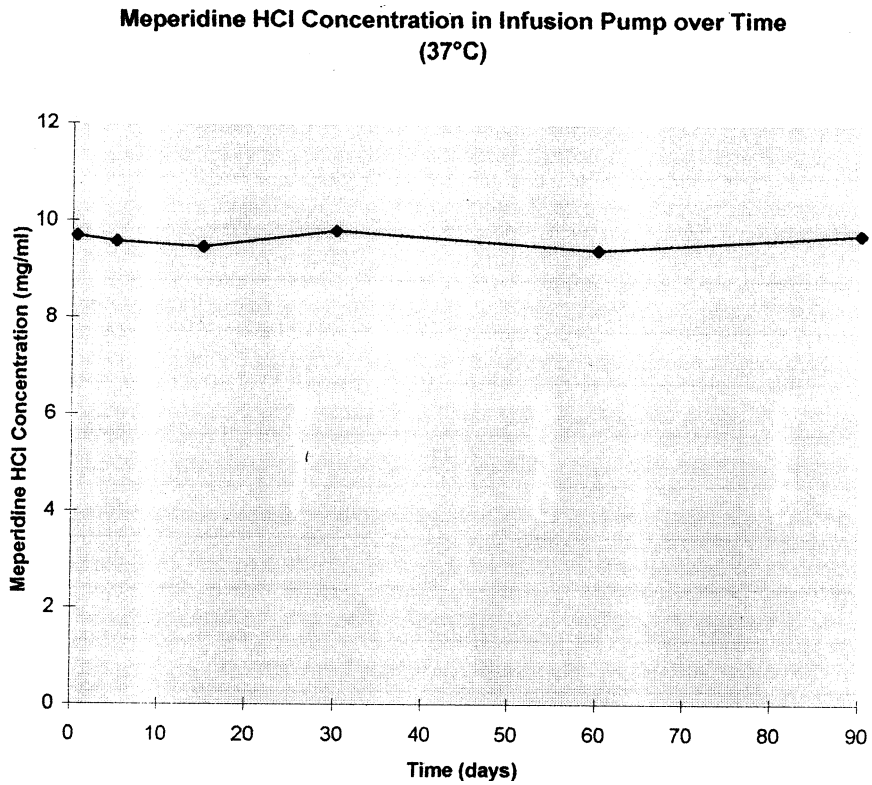

Fig. 3. Plot showing concentration versus time profile of meperidine · HCl stored as a 10 mg ml^{-1} aqueous solution at 37°C in an implantable infusion pump for 90 days. The associated calibration plot ranged from 0–12 μg ml^{-1} meperidine calculated at the HCl salt.

other internal standards reported in the surveyed literature of non-MS–GC methods (see Section 1) cannot be expected to control for potential hydrolytic loss of the analyte. Even the butyl ester homolog of meperidine [18,20] will only equivocally control for any post-sampling drug loss because of the non-equivalent chemical environments about these two esters. The piperidyl labeled [$^2H_4$]-meperidine, as used in the present study, allows for compensation of hydrolytic loss and is commercially available, unlike the [$^2H_5$]-phenyl [26], [$^2H_5$]-ethyl [25], or [$^2H_{10}$]-phenyl ethyl [27,28] labeled meperidine isotopologs.

The molecular ions of meperidine and [$^2H_4$]-meperidine were selected for monitoring in spite of their low relative abundance (Fig. 1); High sensitivity was not a significant concern with the mg ml^{-1} drug concentrations sampled. However, other investigators have found adequate sensitivity when similarly selecting the molecular ion of meperidine for packed column GC–MS analysis of biological samples [26,27]. In those studies, the mass of the intact molecule was monitored in order to avoid chemical interferences detected at lower masses. The ion currents of the high relative abundance decarboethoxylated fragment ions, e.g., m/z 175 for [$^2H_4$]-meperidine, were not selected because unlabeled meperidine also generates a coincident m/z 175 fragment ion, albeit of low abundance.

The pH of the 10 mg ml^{-1} meperidine · HCl solution used in the infusion pump was determined to be 5.83. In kinetic studies at elevated temperatures, pH values of 4.01 [35] or 7.5 [36] have been reported to afford the greatest hydrolytic stability to solutions of meperidine. Thus, the stability of meperidine · HCl evidenced in the pump samples (Fig. 3) should, in part, be attributable to the resulting pH residing between these two reported stability maxima.

5. Conclusion

Packed column GC still retains a modest presence in analytical separation methodology but has largely been supplanted by capillary GC because of inherently superior chromatographic performance (and its ease of interfacing with MS [29]). The present study provides validation of a capillary GC–MS method based on the analytical fundamentals of the Lindberg et al. isotopic dilution packed column approach to meperidine quantitation. The [$^2H_4$]-meperidine used was commercially available unlike most other published meperidine GC–MS methods using deuterated internal standards [25–28].

Application to the described capillary GC–MS method to a pilot stability study of aqueous meperidine · HCl stored at 37°C for 90 days in a surgically implantable infusion pump provided evidence that the drug does not significantly degrade in this device under these conditions. In clinical practice, drug solutions in the pump are seldom used beyond 30–40 days. Accordingly, meperidine · HCl appears to be an acceptable analgesic choice for infusion by this route, especially in those patients who cannot tolerate morphine [8].

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References

[1] T. Reisine, G. Pasternak, in: J.G. Hardman, L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Gilman (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics, ninth ed., McGraw-Hill, New York, 1996, pp. 540–543.
[2] A. Hoekstra, Int. J. Artif. Organs 17 (1994) 151–154.
[3] S.J. Hassenbusch, P.K. Pillay, M. Magdinec, K. Currie, J.W. Bay, E.C. Covington, et al., J. Neurosurgery 73 (1990) 405–409.
[4] G.A. Brazenor, Neurosurgery 21 (1987) 484–491.
[5] R.D. Penn, J.A. Paice, W. Gottschalk, A.D. Ivankovich, J. Neurosurg. 61 (1984) 302–306.
[6] R.D. Penn, J.A. Paice, J. Neurosurg. 67 (1987) 182–186.
[7] J.P. Blount, K.B. Remley, S.K. Yue, D.L. Erickson, J. Neurosurg. 84 (1996) 272–276.
[8] S.C. Harvey, M.G. O'Neil, C.A. Pope, B.G. Cuddy, T.A. Duc, Ann. Pharmacother. 31 (1997) 1306–1308.
[9] T.J. Goehl, C. Davison, J. Pharm. Sci. 62 (1973) 907–909.
[10] J.A. Knowles, G.R. White, H.W. Ruelius, Anal. Lett. 6 (1973) 281–290.

[11] K. Chan, M.J. Kendall, M. Mitchard, J. Chromatogr. 89 (1974) 169–176.
[12] L.E. Mather, G.T. Tucker, J. Pharm. Sci. 63 (1974) 306–307.
[13] H.H. Szeto, C.E. Inturrishi, J. Chromatogr. 125 (1976) 503–510.
[14] M.A. Evans, R.D. Harbison, J. Pharm. Sci. 66 (1977) 599–600.
[15] S.Y. Yeh, H.A. Krebs, J. Pharm. Sci. 70 (1981) 482–486.
[16] T.J. Siek, J. Forensic Sci. 23 (1978) 6–13.
[17] L. Feng, H. Xuying, L. Yi, J. Chromatogr. B 658 (1994) 375–379.
[18] P. Hartvig, K.-E. Karlsson, L. Johansson, J. Chromatogr. 121 (1976) 235–242.
[19] P. Hartvig, K.-E. Karlsson, C. Lindberg, L.O. Boréus, Eur. J. Clin. Pharmacol. 11 (1977) 65–69.
[20] P. Hartvig, C. Fagerlund, J. Chromatogr. 274 (1983) 355–360.
[21] P. Jacob, J.F. Rigod, S.M. Pond, N.L. Benowitz, J. Pharm. Sci. 71 (1982) 166–168.
[22] J. Caldwell, L.A. Wakile, L.J. Notarianni, R.L. Smith, G.J. Correy, B.A. Lieberman, et al., Life Sci. 22 (1978) 589–596.
[23] E.L. Todd, D.T. Stafford, J.C. Morrison, J. Anal. Toxicol. 3 (1979) 256–259.
[24] C. Lindberg, M. Berg, L.O. Boréus, P. Hartvig, K.-E. Karlsson, L. Palmér, et al., Biomed. Mass Spectrom. 5 (1978) 540–543.
[25] G. Tomson, R.I.M. Garle, B. Thalme, H. Nisell, L. Nylund, A. Rane, Br. J. Clin. Pharmacol. 13 (1982) 653–659.
[26] P.G. Quinn, B.R. Kuhnert, C.J. Kaine, C.D. Syracuse, Biomed. Environ. Mass Spectrom. 13 (1986) 133–135.
[27] R.K. Verbeeck, R.C. James, D.F. Taber, B.J. Sweetman, G.R. Wilkinson, Biomed. Mass Spectrom. 7 (1980) 58–60.
[28] R.J. Herman, C.B. McAllister, R.A. Branch, G.R. Wilkinson, Clin. Pharmacol. Ther. 37 (1985) 19–24.
[29] G.M. Message, Practical Aspects of Gas Chromatography/Mass Spectrometry. Wiley, New York, 1984.
[30] V.P. Shah, K.L. Midha, S. Dighe, I.J. McGilveray, J.P. Skelly, A. Yacobi, et al., J. Pharm. Sci. 18 (1992) 309–312.
[31] D.R. Knapp, Handbook of Analytical Derivatizations Reactions, Wiley, New York, 1979.
[32] N.P. Fish, N.J. DeAngelis, in: K. Florey (Ed.), Analytical Profiles of Drug Substances, vol. 1, Academic Press, New York, 1972, p. 191–202.
[33] C. Lindberg, K.-E. Karlsson, P. Hartvig, Acta. Pharm. Suec. 15 (1978) 327–336.
[34] I.W. Wainer, J.E. Stambaugh, J. Pharm. Sci. 67 (1978) 116–118.
[35] R.M. Patel, T.-F. Chin, J.L. Lach, Am. J. Hosp. Pharm. 25 (1968) 256–261.
[36] O.M. Marelli, Rend. 1st Super. Sanita (Rome) 14 (1951) 282–286.