DETERMINATION OF MEPERIDINE (PETHIDINE) IN BODY FLUIDS BY GAS CHROMATOGRAPHY WITH SURFACE IONIZATION DETECTION

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原　　報

DETERMINATION OF MEPERIDINE (PETHIDINE) IN BODY FLUIDS BY GAS CHROMATOGRAPHY WITH SURFACE IONIZATION DETECTION

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表面電離検出ガスクロマトグラフィーによる体液中メペリジン（ペチジン）の測定

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Summary

Meperidine (pethidine) could be measured with high sensitivity by gas chromatography (GC) with surface ionization detection (SID) with diphenylpyraline as an internal standard. The calibration curve showed linearity in the range of 20—1000 pg on column. The detection limit of meperidine was 10 pg on column (0.5 ng per ml of a sample). The sensitivity of GC-SID was more than one order of magnitude higher than that of GC-nitrogen-phosphorus detection. A detailed procedure for isolation of the drugs from human whole blood and urine with use of Sep-Pak C_{18} cartridges before GC-SID is also presented. The recovery of meperidine was close to 100 %.

Key words : Meperidine ; Pethidine ; Diphenylpyraline ; Gas chromatography ; Surface ionization detection ; Sep-Pak C_{18} cartridges

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Introduction

Meperidine (pethidine) is a narcotic analgesic drug, which is widely used in therapeutic practice. For analysis of meperidine in biological samples, gas chromatography (GC) with nitrogen-phosphorus detection (NPD) has been usually employed [1, 2]. In 1985, Fujii and Arimoto first introduced surface ionization detection (SID) for GC [3], and it was suggested to be very sensitive and specific especially to tertiary amines. Application of GC-SID has recently started for some kinds of drug groups [4-9]. The present paper describes a highly sensitive gas chromatographic method with SID for meperidine with diphenylpyraline as an internal standard (IS). A detailed procedure for isolation of the drug from human whole blood and urine is also presented.

Experimental

Materials

Chemical structures of meperidine and diphenylpyraline (IS) are shown in Fig. 1. Meperidine hydrochloride was donated from Tanabe Seiyaku Co., Ltd., Osaka; diphenylpyraline hydrochloride from Sigma Chemical Co., St. Louis, MO, USA. Sep-Pak C_{18} cartridges was purchased from Waters Associates, Milford, MA, USA., and a DB-17 fused silica capillary column (15m × 0.32 mm i.d., film thickness 0.25 μm) from J & W Scientific, Folsom, CA, USA. Other common chemicals used were of the highest purity commercially available. Whole blood and urine were obtained from healthy subjects.

Isolation with Sep-Pak C_{18} cartridges

Procedures for pretreatment of Sep-Pak C_{18} cartridges and for extraction of meperidine and IS spiked in whole blood and urine samples were exactly the same as described in our previous report [9].

GC conditions

GC was carried out on a Shimadzu GC-14A gas chromatograph equipped with SID and on a Hewlett-Packard Model 5890 gas chromatograph with NPD. A DB-17 fused silica capillary column and a split-splitless injector were used. The GC conditions were : column temperature, 100—220 °C (2 min hold at 100 °C/min) ; injection temperature, 240 °C ; and helium flow rate 3

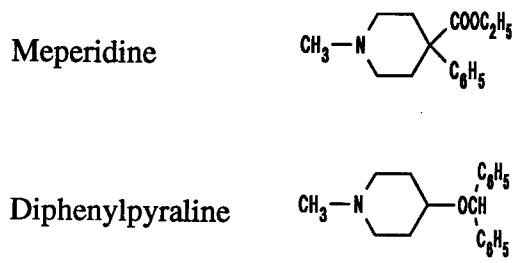

Fig. 1. Chemical structures of meperidine and diphenylpyraline (IS).

ml/min. The SID conditions were : detector temperature, 280℃ ; heating current through the platinum emitter, 2.2 A ; emitter temperature, *ca.* 600 ℃ ; and ring electrode bias voltage, +200 V with respect to the collector electrode. The samples were injected in the splitless mode at a column temperature of 100 ℃ and the splitter was opened after 2 min.

Results

Figure 2 shows gas chromatograms by GC-SID for whole blood and urine samples with and without addition of meperidine (50 ng) and diphenylpyraline (100 ng). The drug peaks did not overlapped any impurity peaks. The retention times were 8.7 min for meperidine, and 12.8 min for diphenylpyraline. The recovery of meperidine was close to 100 % for both samples ; that for diphenylpyraline was 84.3 and 82.1 % for whole blood and urine samples, respectively. The baseline remained steady during increase in column temperature.

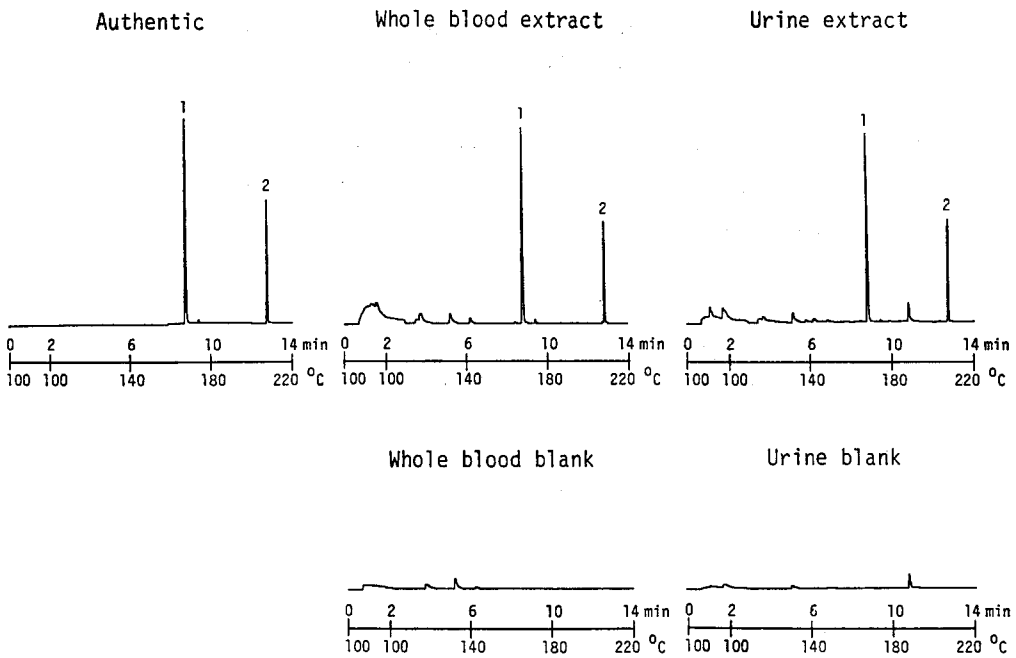

Fig. 2. Capillary GC-SID for meperidine (peak 1) and diphenylpyraline (peak 2) extracted from whole blood and urine, and their backgrounds, using Sep-Pak C_{18} cartridges for isolation. GC was carried out with a fused silica DB-17 capillary column (15m ×0.32 mm i.d., film thickness 0.25 μm). GC conditions were : column temperature, 100—220 ℃ (10 ℃/min) ; injection temperature, 240 ℃ ; detector temperature, 280 ℃ ; helium flow rate 3 ml/min. The samples were injected in the splitless mode at a column temperature of 100 ℃ and the splitter was opened after 2 min. The mixture of meperidine (50 ng) and diphenylpyraline (100 ng) was added to 1 ml of whole blood or urine.

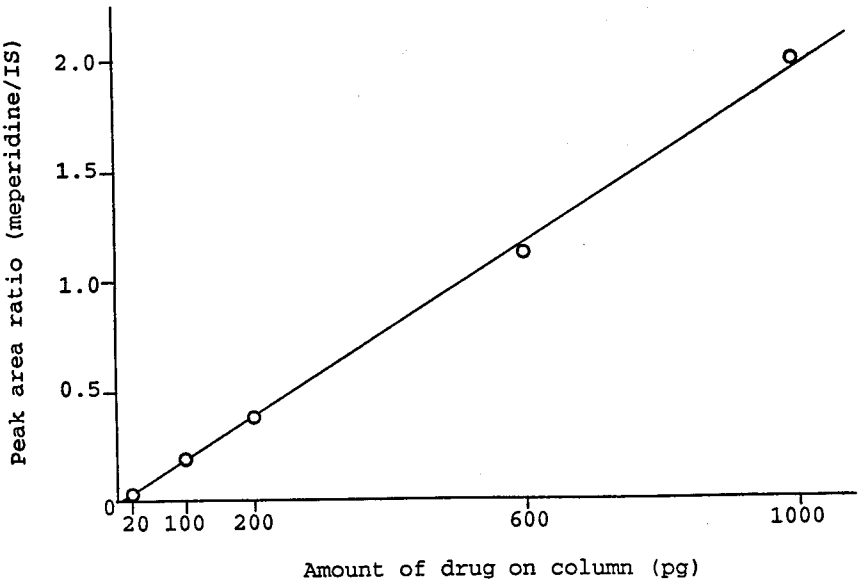

Fig. 3. Calibration curve for meperidine with diphenylpyraline as IS. The vertical axis shows the peak area ratio expressed as meperidine to IS (2 ng on column). GC conditions were as specified in Fig. 2.

The calibration curve for meperidine, with diphenylpyraline as IS, is shown in Fig. 3. It showed linearity in the range of 20—1000 pg on column. The equation and r values for the curve were : $y=0.00199x-0.0245$, $r=0.9993$. The detection limit was 0.5 ng/ml of a sample (10 pg on column).

The samples were also subjected to GC-NPD under the same conditions for comparison. Many impurity peaks appeared especially in urine sample by GC-NPD. The sensitivity of GC-NPD was more than one order of magnitude higher than that of GC-NPD.

Discussion

In the present study, we have demonstrated that meperidine, a narcotic analgesic drug, can be detected with high sensitivity by GC-SID. Meperidine contains a methylpiperidine ring in its structure (Fig. 1), which may cause high response to the SID. As an internal standard for the drug, we have selected diphenylpyraline, an antihistaminic drug, which also contains a methylpiperidine ring and a phenyl group. In the original report by Fujii and Arimoto [3], tertiary amino compounds, such as tributylamine and triethylamine, gave very high response to SID, suggesting that tertiary amino group with straight side chain structures gives the highest sensitivity by this method. However, according to the progress of our studies on GC-SID for various compounds [5, 7-9], it has become more obvious that tertiary amino compounds with ring structures often give relatively high response to SID. The typical examples are dextromethorphan

and dimemorphan, the morphine analogues [9], and the present narcotic meperidine. Studies on detection of other narcotics with cyclic tertiary amino groups by GC-SID are now under way in our laboratories.

We have carefully compared the sensitivity by GC-SID with that by GC-NPD for meperidine ; that of the former was more than ten times higher than that of the latter, when judged with signal-to-noise ratios and baseline stability. In our previous studies, such higher sensitivity by GC-SID than that by GC-NPD could be equally obtained for tricyclic antidepressants [4], local anesthetics [5, 6], phenothiazines [7], diphenylmethane antihistaminics [8] and morphine-analogue antitussives [9], which are all tertiary amino compounds. However, secondary amino compounds, such as terodiline, give 10—100 times lower sensitivity by GC-SID [8] ; GC-NPD may give better results for the secondary amines.

Therapeutic concentration of meperidine in human plasma was reported 200—800 ng/ml, and toxic effects are usually associated with blood concentrations greater than 2000 ng/ml [10]. Since the detection limit of the present GC-SID for meperidine (0.5 ng/ml) is far below the above therapeutic and toxic levels, this method may also allow trace determination of meperidine present in small samples, such as blood stains and hair, extending its applicability in forensic and clinical toxicology.

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