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Note

Gas chromatography–electron-impact and chemical-ionization mass spectrometry of haloperidol and its chlorinated homologue

M. A. MOULIN, R. CAMSONNE, J. P. DAVY*, E. POILPRE*, P. MOREL*, D. DEBRUYNE and M. C. BIGOT

Department of Pharmacology, University Hospital Center of Caen, 14040 Caen Cedex (France)

and

M. DEDIEU and M. HARDY

Laboratory of Applied GC–MS, Ribermag, 49 Quai du Halage, 92502 Rueil Malmaison (France)

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Despite its two halogenated electrophilic species, the electron-capture detector response of haloperidol[1] (HAL) in gas chromatography is poor[2–4]. In this paper, electron-impact (EI) and chemical-ionization (CI) mass spectra of HAL and chlorine-substituted haloperidol (HAC) are presented and an approach to their detection by gas chromatography–mass spectrometry (GC–MS) using selective-ion monitoring[5] (SIM) is described. The characteristics of SIM are a very high sensitivity and selectivity[6,7], which are needed for low concentration level measurements in complex mixtures.

EXPERIMENTAL

Instrumentation

GC–MS was performed on a Ribermag EI–CI R 10-10 B quadrupole mass spectrometer using a Riber 400 computer system and a Girdel Model 30 gas chromatograph (Ribermag, Rueil Malmaison, France). High-resolution chromatography was performed on (a) 15 m × 0.25 mm I.D., 0.15-μm SE-30 and (b) 25 m × 0.25 mm I.D., 0.2-μm OV-17 wall-coated open-tubular (WCOT) glass columns (Chrompack, Les Ulis Orsay, France) at 260° and 270° (isothermal), respectively. The temperature of the solid glass injector was 280° and the carrier gas (helium) flow-rate was 2.5 ml/min. The integration times were (a) for mass spectra, 3 msec/a.m.u. and (b) for fragmentography, 5 × 100 msec for the *m/e* 224 and 237 peaks. In the CI mode, isobutane was used as reactant gas at a pressure of 1 torr.

Chemicals

HAL {1-[3-(4-fluorobenzoyl)propyl]-4-hydroxy-4-(4-chlorophenyl)piperidine} and HAC {1-[3-(4-chlorobenzoyl)propyl]-4-hydroxy-4-(4-chlorophenyl)piperidine} were kindly supplied by Janssen Pharmaceutica, Beers, Belgium. The purity of both

* Department of Psychiatry.

products, checked by WCOT column GC–MS, was more than 99.7%. When stored in darkness at room temperature, these compounds showed no signs of decomposition.

Other chemicals used were of analytical-reagent grade (E. Merck, Darmstadt, G.F.R.).

RESULTS AND DISCUSSION

EI mass spectrum

Full mass spectra were obtained from the injection of 10 ng of HAL or HAC. They showed for HAL (Fig. 1a) a molecular ion (M^+) of extremely weak intensity at *m/e* 375 with major ions at *m/e* 237, 224 (base peak), 206, 123 and 42, and for HAC (Fig. 1b) an M^+ peak at *m/e* 391 and other ions at *m/e* 341, 281, 237, 224 (base peak), 206, 190, 139, 111, 56 and 42.

From the occurrence of the natural isotopes ^{35}Cl (isotopic abundance 0.75529) and ^{37}Cl (isotopic abundance 0.24471), ion-pair fragments containing one chlorine atom at *m/e* 237–239 and 224–226 were easily recognized[8] and constitute ions of interest for HAL and HAC. The mass spectrum of HAL obtained with a Varian-MAT 44 mass spectrometer (Varian, Orsay, France) (Fig. 1c) is, as expected, comparable to those seen above and from a library[9] (in which the mass spectrum of HAC is not presented) but with a slight difference in intensity.

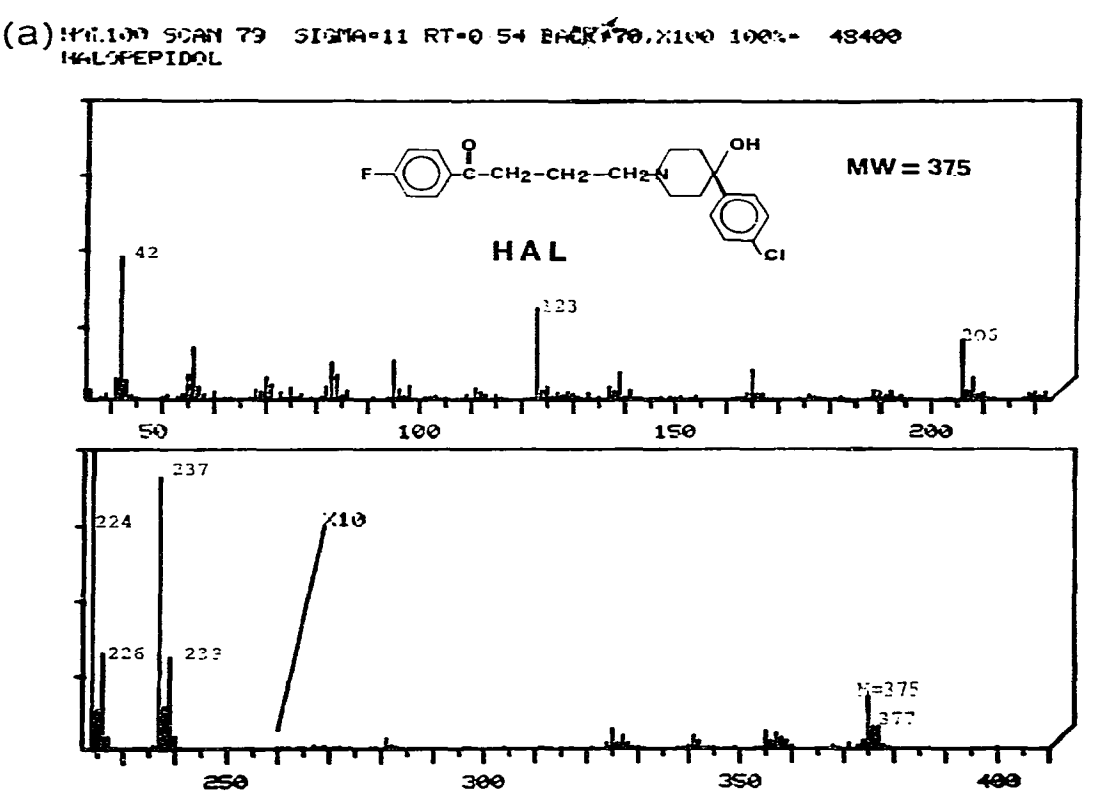

Fig. 1.

(Continued on p. 326)

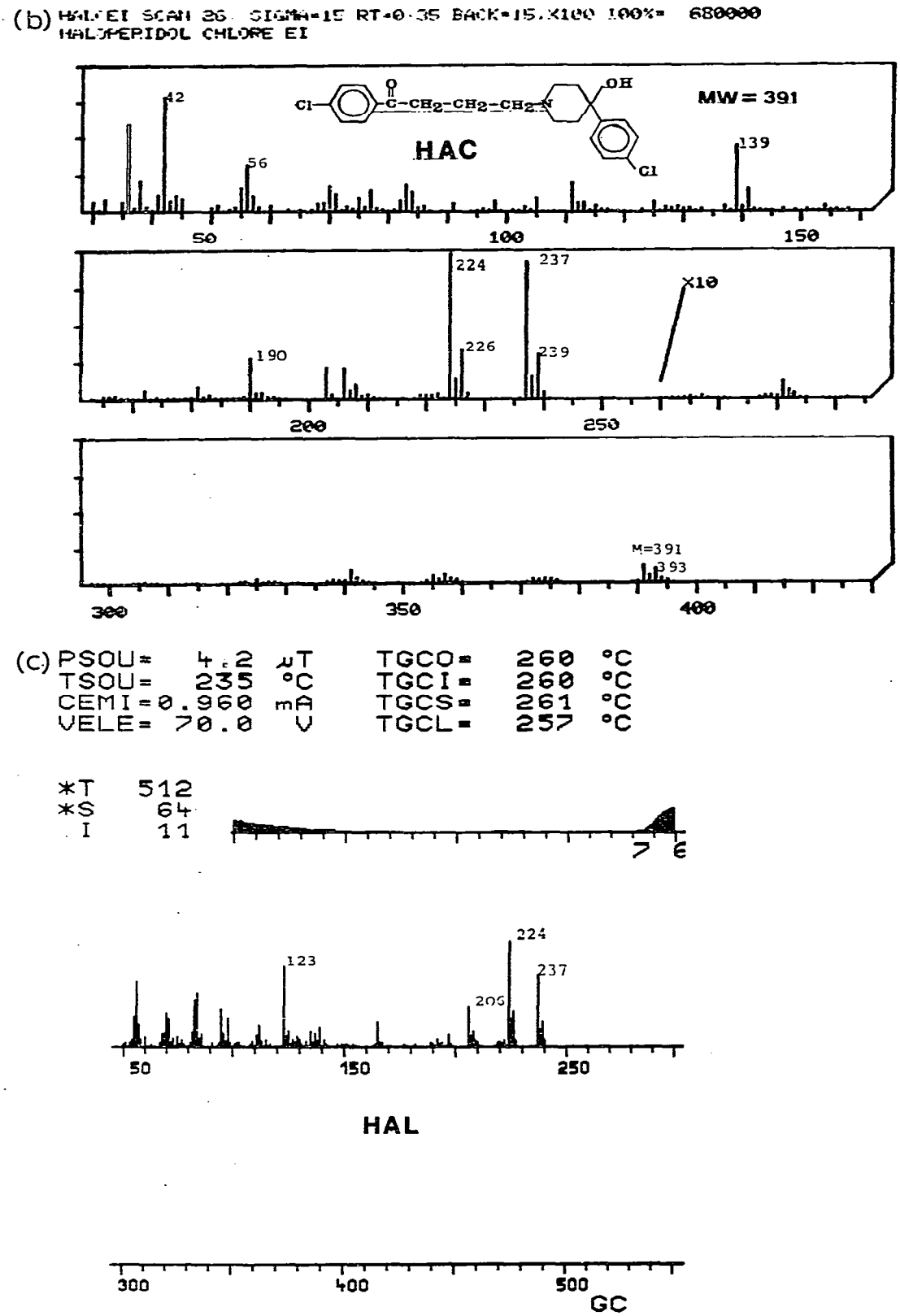

Fig. 1. EI mass spectra of (a) HAL, (b) HAC and (c) HAL obtained with Riber 10-10 B and Varian-MAT 44 mass spectrometers, respectively.

CI mass spectrum

Ion doublets at *m/e* 237–239 and 224–226 were also present in the isobutane CI mass spectra of HAL (Fig. 2a) and HAC (Fig. 2b). The peaks observed previously at *m/e* 375 (Fig. 1a) and 391 (Fig. 1b) were shifted by one mass unit (M+1) as a result of proton addition to give *m/e* 376 for HAL and *m/e* 392 for HAC. These quasimolecular ions (M+1) also constitute base peaks and if needed could be used for quantitative mass fragmentography. They were characterized by the presence of one chlorine atom (HAL) at *m/e* 376 and 378 (intensity ratio 1:3) and two chlorine atoms (HAC) at *m/e* 392 and 394 (intensity ratio 2:3). The minimal sample ion fragmentation, enhanced quasi-molecular ion (M+1) and the presence of the ion M + 43 (Figs. 2a and b) are typical of isobutane CI spectra which serve for ready reference. In the direct sample introduction mode for mass spectrometry the melting point of HAL and HAC was about 142°.

Mass fragmentograms of ions of interest

Common ion fragments at *m/e* 224.2 and 237.2 were used for the fragmentographic analysis of HAL and HAC, which have different retention times, since these fragments were two of the largest peaks in the spectra obtained in the EI mode. In order to avoid possible interferences and to improve the sensitivity with a view to the analysis of low levels of HAL in complex mixtures or serum, high-resolution chromatography[10] was performed. When the SE-30 WCOT column was used at 260°, the retention time of HAL was 1.8 min and that of HAC was 3.25 min. The tailing peaks, in spite of short retention times, are similar to those obtained with the OV-17 WCOT column at 270°. In the latter instance the retention times of HAL and HAC were 7.18 and 12.7 min, respectively. Typical SIM plots for HAL and HAC (ions at *m/e* 224.2 and 237.2; OV-17 WCOT column) are shown in Fig. 3a. The minimal detectable amounts of both HAL and HAC for a signal-to-noise ratio of 3:1 were 200 pg in the OV-1 and 100 pg in the OV-17 WCOT columns. Some adsorption occurred, but to a lesser extent in the latter column. For this purpose, HAL or HAC might be used in glass capillary column absorption tests needed in any quantitative work at levels below 1 ng. Certainly HAL or HAC was not completely eluted from these columns. Asymmetric peaks were observed at low levels (Fig. 3a), although symmetric peaks can be obtained at the 100-ng (heavy loading of the SE-30 capillary column) or 1-μg level in a 3% OV-17 packed column at 260°, with nitrogen flame-ionization detection (unpublished results). The solid glass injector and other elements of the ion source may be partly involved. The expected high sensitivity at the 1–10-pg level of SIM has so far not been attained.

Despite this deficiency, which must be overcome in the establishment of a definitive GC–MS reference method for HAL or HAC (*i.e.* choice of suitable glass support, liquid phase, film thickness and derivatization or isotopic dilution procedure), serum levels of HAL were tentatively determined using an OV-17 WCOT column with HAC as the internal standard, using 200–500-μl serum samples taken from psychotic patients given high (18 mg/day) and low (4 mg/day) doses (Fig. 3b). The sera (extracted once with 5 ml of alkaline diethyl ether and the residue dissolved in 50 μl of methylene chloride) were found to contain 28.2 $\pm$ 1.9 and 9.5 $\pm$ 0.9 ng/ml of HAL, respectively.

Non-linear adsorption at the nanogram level is the main problem affecting the accuracy of the GC assay of butyrophenones.

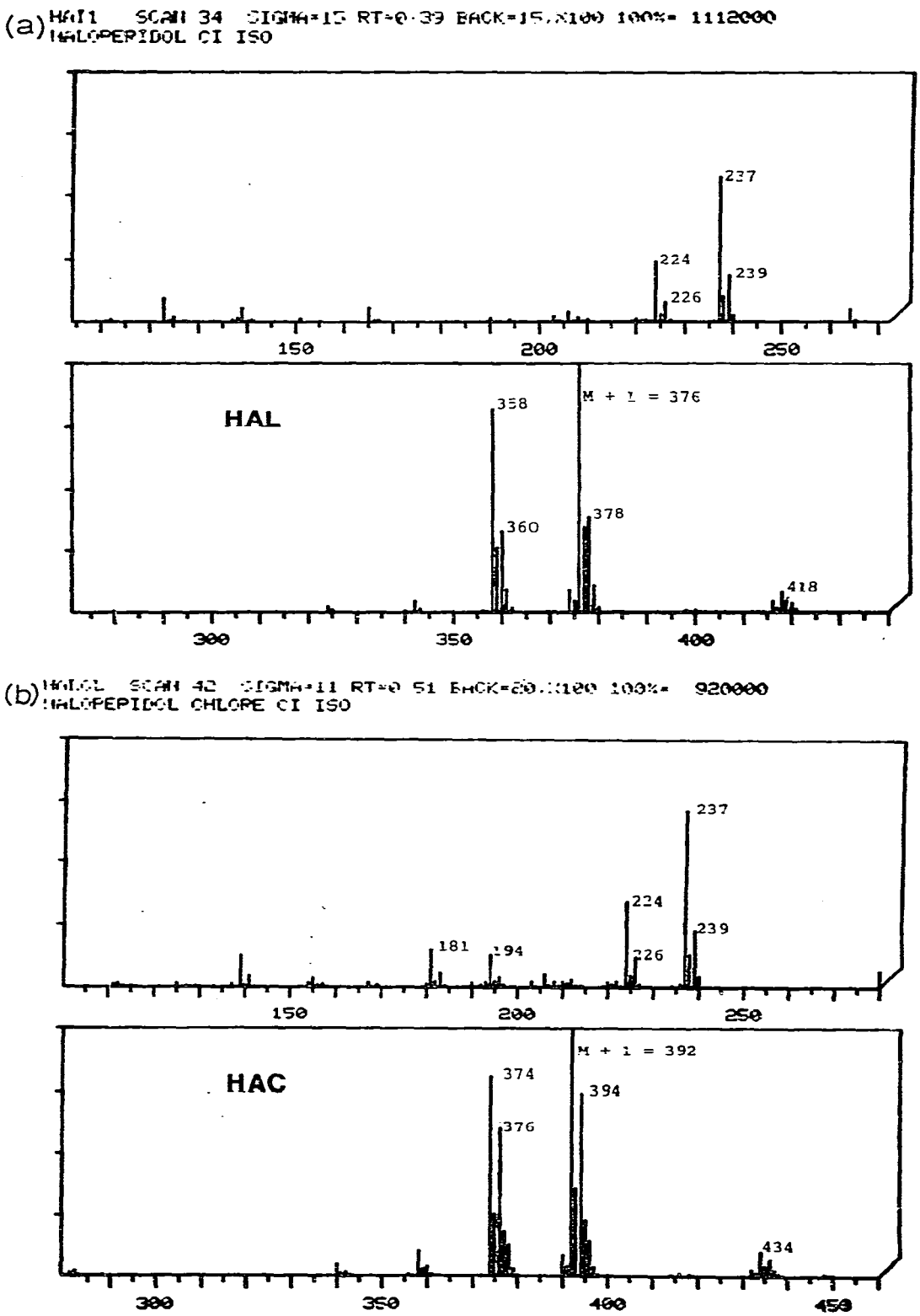

Fig. 2. CI mass spectra of (a) HAL and (b) HAC.

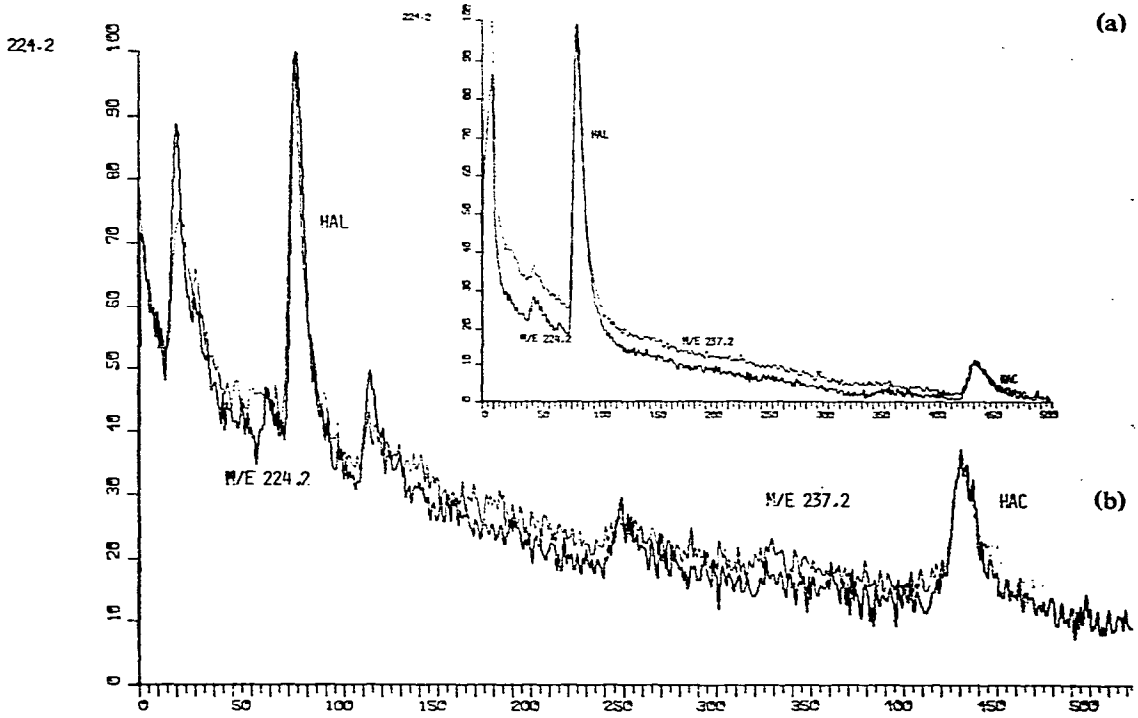

Fig. 3. Mass fragmentogram of common ions of interest (*m/e* 224.2 and 237.2) of HAL and HAC used as internal standard in (a) standardization and (b) patients' serum (200 μl of sample and 2 μl of extract equivalent to 225 pg of HAL and 100 pg of HAC were evaporated into the solid glass injector and then injected into the chromatograph.

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