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Selective determination of haloperidol in human serum: surface ionization mass spectrometry and gas chromatography with surface ionization detection

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Abstract

Surface ionization organic mass spectrometry (SIOMS) has been performed on the clinically important drug haloperidol using quadrupole mass spectrometry in which the thermal ion source has a rhenium oxide emitter. The surface ionization (SI) mass spectrum is presented, interpreted in a purely empirical way by means of evidence from previous investigations, and then compared to results from conventional electron impact (EI) ionization. An approach to detection of this drug in serum by gas chromatography (GC) with a surface ionization detector (SID) and GC–SIOMS is described. This approach demonstrates that (a) haloperidol is efficiently surface-ionized, giving a unique SI mass spectrum, (b) experimental results rationalize the combined sensitivity and selectivity of the GC–SID for the examined drug, (c) the detection limit for haloperidol in serum is 1.1 ng/ml ($S/N=3$) by GC–SID (the coefficients of variation of the assay are generally low, i.e. below 8.5%) and (d) the GC–SIOMS coupling can be used for sensitive and selective detection of haloperidol in serum.

Keywords: Haloperidol

1. Introduction

Haloperidol is a neuroleptic antidepressant used widely in current clinical practice [1]. The therapeutic concentration of haloperidol in serum was re-

ported to be in the range of 4–20 ng/ml [2] and toxic effects may occur with blood concentrations greater than about 0.05 $\mu\text{g/ml}$ [3,4]. Therefore, there is a great need for the development of good analytical methods to monitor haloperidol serum levels.

A number of haloperidol assays have been developed using radioimmunoassay [5] and a stripping voltammetric method [6]. Gas chromatography (GC)

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has been used with electron capture [7] or nitrogen-specific [2,8] detection, as has high-performance liquid chromatography with UV [9] and electrochemical detection [10]. However, these methods are prone to problems of sensitivity and/or lack of specificity, mainly due to interference from coeluting compounds.

A number of papers [11–13] have appeared describing the use of gas chromatography–mass spectrometry (GC–MS) for haloperidol analysis. The use of combined GC–MS made it possible to obtain the required specificity by monitoring the identity of the peaks as they eluted from the gas chromatograph. With a quadrupole MS equipped with an electron ionization source, selected-ion monitoring, in general, brought the sensitivity for the drug in blood serum into the 5–10 ng/ml range using an internal standard for quantitation [14].

GC–MS has also been used with a chemical ionization technique [15]. This provides for better combined selectivity and sensitivity than obtained using previous assays. However, despite the number of mass spectrometric procedures available [16,17], determination of serum concentrations of drugs encountered in patients receiving small dosages is still not universal or perfect. The measurement of low levels of drugs in biological samples may require a new complementary method. This will be the subject of the present study.

Surface ionization (SI) has proven to be a useful technique for MS [18] and GC [19,20]. With SI, some organic molecules can be ionized with high efficiency. The preliminary GC studies with a surface ionization detector (SID) revealed that haloperidol is a drug for which SI can be successfully applied to complement conventional techniques. Hence, we are now in the process of comprehensively evaluating the surface ionization techniques combined with GC and MS for the analysis of haloperidol. The mass spectrometric approach allows consistent rationalization of the SID results.

This paper describes a new assay method for the analysis of haloperidol levels in serum without any concentration procedure, utilizing GC with SID (as low as 1.1 ng/ml) and GC–SIOMS (surface ionization organic mass spectrometry). The basis of the present assay is rationalized through the SI mass

spectrum obtained by SIOMS, demonstrating the analytical power of SI techniques.

2. Experimental

2.1. Apparatus

The experimental set-up for GC–SIOMS has been reported in detail elsewhere [21,22]. Briefly, a dual EI–SI mass spectrometer coupled to a gas chromatograph was used (Finnigan Model 3300, Sunnyvale, CA, USA). The SI source assembly was laboratory-made so that the Re-oxide emitter could be fitted into the center of the EI ion source chamber when the assembly was inserted. Analysis was carried out in the SI mode with O₂ added continuously through the gas flow line to allow preparation of rhenium oxide and an increase in work function at the emitter surface. The abundance of product ions in the SI mode is variable and predominantly dependent on the surface temperature, T_s . In this study, T_s was set at 830°C which gives the maximum ion signal for haloperidol. In the EI mode, the electron emission current was 0.7 mA with an electron energy of 55 eV. EI and SI mass spectra were generated for the haloperidol sample. These were analyzed individually. About 100 µg of solid sample was placed in a glass holder which was located in a GC oven about 20 cm away from the ion chamber of the EI source. The desired amount of sample was controlled by varying the GC oven temperature (about 142°C). Full mass spectra were acquired by scanning the mass range m/z 450–30 approximately once per 10 s.

The GC system [20,22] consisted of a gas chromatograph (Shimadzu Model GC-15APF, Kyoto, Japan) fitted with a Van den Berg-type solventless injector and a surface ionization detector with an electrically heated Pt emitter (Shimadzu Model SID-14/15). The analytical conditions are summarized in Table 1.

2.2. Reagents

The haloperidol sample investigated in this study, along with the proposed thermal dissociation patterns, is shown in Fig. 1. The drug, purchased from

Table 1
Analytical conditions

Apparatus:	Finnigan GC-MS system with a combined EI-SI ion source (Model 3300) and Shimadzu GC with NPD and SID detectors (Model GC-15APF)
Injector:	Van den Berg-type solventless injector
Column:	DB-1, fused-silica capillary column, (methyl silicone) 30 m×0.31 mm I.D., 1 μm film thickness, operated at 300°C
Carrier gas:	He, 3.4 ml/min
Split gas:	He, 4.8 ml/min
Purge gas:	He, 46 ml/min
Make-up gas:	He, 50 ml/min
Air flow gas:	200 ml/min (only for SID operation)

Yoshitomi Pharmaceutical (Kyoto, Japan) was used without further purification.

2.3. Standardization

To obtain reference data and to enable standardization of analysis, a series of drug solutions

(with concentrations of 1 to 500 μg/ml) were prepared in chloroform for GC-SID and GC-SIOMS. The accuracy, precision and recovery were tested with serum samples prepared by adding the drugs to a serum pool previously tested to be negative for haloperidol. The linearity of the calibration curves was examined over the chosen range

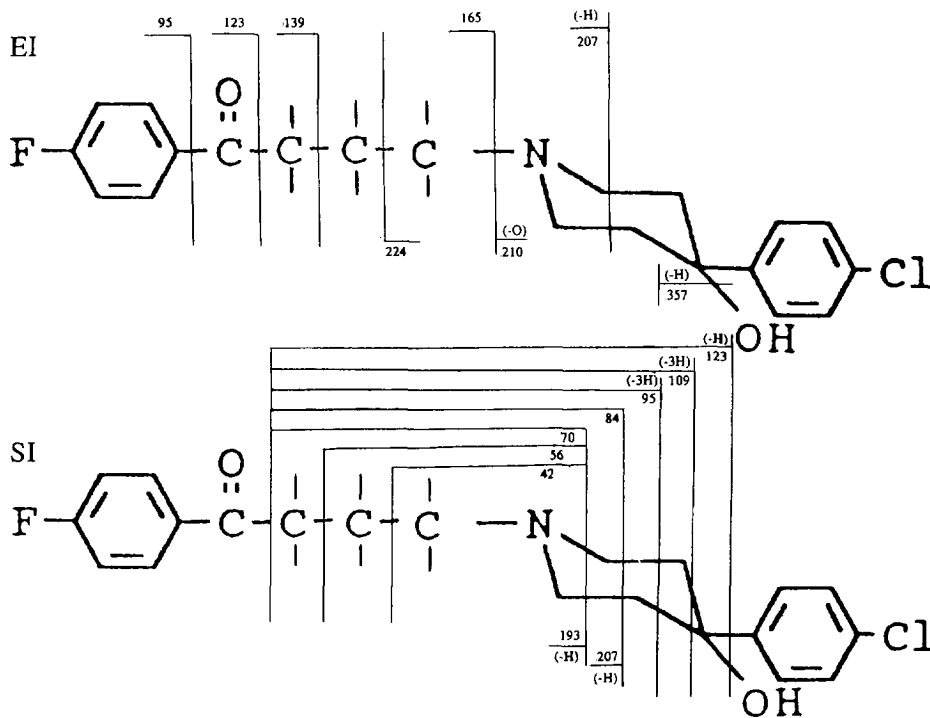


Fig. 1. Structure of the haloperidol molecule along with the proposed (upper panel) EI cleavage scheme and (lower panel) thermal dissociation patterns followed by SI.

of 1 to 500 ng/ml plasma sample, with bromperidol included as an internal standard. A plot of seven concentrations of haloperidol in plasma against their corresponding peak heights produced a straight line with a certainty $\pm 3.8\%$. These control samples were prepared in advance from the same plasma pool. They were spiked with bromperidol to give a concentration of 250 ng/ml.

2.4. Procedures

A simple and rapid extraction procedure without any concentration was employed for the determination of haloperidol in human serum. This could be completed in less than 30 min. The procedures are as follows: (1) for the internal standard, spike 0.5 ml of serum with 100 μl of a 1.25 $\mu\text{g}/\text{ml}$ chloroform solution of bromperidol (ca. 250 ng/ml plasma); (2) to each add 0.1 ml of 1 M NaOH and 400 μl of chloroform; (3) shake for 3 min and then centrifuge at 12 000 rpm for 20 min; (4) inject 10 μl of an

extraction chloroform solution into a GC port with a syringe.

3. Results and discussion

3.1. Mass spectrometric considerations

3.1.1. SI and EI mass spectra

Fig. 2 shows the mass spectra (scan mass range 30 to 450 a.m.u.) obtained by EI (upper column) and SI (lower column). The SI spectrum was interpreted in a purely empirical way and was characterized and compared to the conventional EI spectrum in order to illustrate the potential and the limitations of the SI technique for the analysis of drug molecules. These full mass spectra also make it possible to choose suitable ions for selected-ion monitoring and to ensure maximum sensitivity for quantitative purposes.

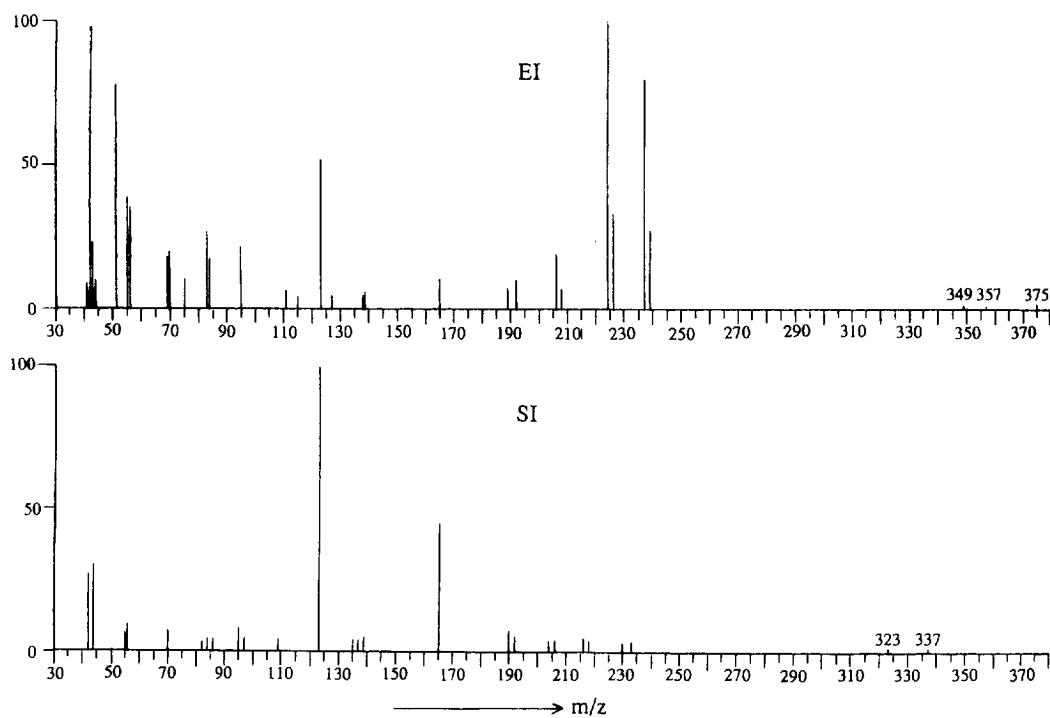


Fig. 2. SI and EI mass spectra of haloperidol. M, parent nominal mass. Only peaks higher than 2% relative to the base peak are listed, except for some small peaks in the high mass range. m/z 42, $[\text{H}_2\text{C}=\text{N}=\text{CH}_2]^+$; m/z 56, $[\text{H}_2\text{C}=\text{N}-\text{CH}_2=\text{CH}_2]^+$; m/z 70, $[\text{H}_2\text{C}=\text{N}-(\text{CH}_2)_2=\text{CH}_2]^+$; m/z 84, $[\text{H}_2\text{C}=\text{N}-(\text{CH}_2)_3=\text{CH}_2]^+$; and m/z 111, $[\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{N}(\text{C}_2\text{H}_5)_2]^+$.

EI. The EI spectrum exhibits a detectable parent M^+ ion and many intense fragment ions. The base peak occurs at m/z 224, while a major fragment appears at m/z 237. At least three other smaller, but significant, fragments appear in the mass range above 237. These spectra are comparable to those reported in Ref. [23] but have a difference in intensity and they are somehow different from those of Ref. [24].

Consistent interpretation of signals in the EI spectrum can be conceived by using relatively conventional pathways. The signal at m/z 357 is readily associated with $[M-H_2O]^+$ fragments. The product ion at m/z 357 has an accompanying chlorine isotope contribution at m/z 359, signifying that this ion retains the chlorophenyl moiety. Also, product ions at m/z 206, 224, 237 and 349 show such an accompanying isotope contribution, indicating that charge is retained on the chlorophenyl portion of the molecule.

Haloperidol displayed a product ion at m/z 165. This corresponds to a fragmentation of the alkyl carbon–nitrogen bond with expulsion of the nitrogen-containing moiety as a neutral and the fluorobenzoyl containing moiety as an ion [25]. This is particularly supported by the lack of contribution of ^{37}Cl isotope peaks. There was evidence of dissociation occurring between the fluorobenzoyl and the alkyl carbon of the hydrocarbon chain. This was confirmed by inspection of the product ion spectrum which only contained a single product ion at m/z 123.

Some other major product ions at m/z 42, 56, 70 and 84, as well as minor ions at m/z 111 are structurally postulated in the caption of Fig. 2.

SI. The SI spectrum illustrates the features one expects from the SIOMS of biomolecules [26]; that is, relatively complex and with many product ions. We have initiated a systematic study of molecules to deal with the problem of spectrum interpretation in a purely practical way. At the same time, we elaborate on a set of tentative hypotheses about ionization in SIOMS [26]. So far, this approach has permitted the consistent rationalization of results.

Our tentative hypotheses about ionization in SIOMS represent an empirical approach, which is primarily intended to enable a structural assignment of the detected signals. Essentially, the final result of

ionization processes is rationalized in terms of the ionization energy of dissociated species and work function of the surface. Key assumptions concern the initial dissociation of molecules on the surface and subsequent competition between ionizations. The hypothesis is characterized by the extensive thermal dissociation on the hot emitter surface, which is followed by surface ionization of thermally dissociated products. The approach to structure interpretation of the signals in SIOMS is based on this mechanism (refer to Fig. 2).

The SI mass spectrum illustrates that, unlike the EI spectrum, there are no molecular ions, but there are many ionic species over the entire mass region with the most intense ions at m/z 123. The expected ionization of the thermally dissociated species is clearly present. Quite a few abundant ionic species appear such as: m/z 42 $[\text{CH}_2\text{NCH}_2]^+$, 56 $[\text{C}_2\text{H}_4\text{NCH}_2]^+$, 70 $[\text{C}_3\text{H}_6\text{NCH}_2]^+$ or $[\text{C}_2\text{H}_4\text{NC}_2\text{H}_4]^+$, and 84 $[\text{C}_3\text{H}_6\text{NC}_2\text{H}_4]^+$. These abundant peaks of the alkylamine group fit the evidence from other SI data of amine compounds [18]. Also, signals at 95, 109, 123, 192 and 206 may possibly correspond to structure-specific losses of side chains from haloperidol (Fig. 2). In this respect, the SIOMS results certainly contain some structural information, which is fairly accessible and, hence, the SI results are useful for diagnostic analysis.

Some signals of higher-mass-range peaks, however, can not be reasonably assigned; for instance, the signal peaks at m/z 190, 204, 216, 218, 230, 232, 323 and 337 in the spectrum. Establishment of a link with the structure becomes less accessible. This is due to the tendency to undergo a complex thermal dissociation process with skeletal rearrangement.

3.1.2. EI vs. SI spectra

By comparison, the SI mass spectrum presented in Fig. 2, which is basically different (unfamiliar) from that of EI, demonstrates the base peak at m/z 123. It is also clear that EI yields small M^+ ions, while SI does not yield any ions in the molecular region. The preference of amino functional groups in a molecule is clearly indicated in SI, whereas EI mass spectrometry gives many ion doublets at m/z 206–208, 224–226, 237–239, 357–359 and 375–377. These peaks are clearly distinguishable as having a chlorine isotope contribution.

Next, we considered the ionization efficiency of the SI method. Since the present ion source is of the combined type [18], it is very easy to compare the ionization efficiencies in the SI and the EI mode. To provide an estimate of the efficiency of this method, the ion yield of base peak ions from SI was compared with that from EI in terms of SI/EI.

The SI(m/z 123)/EI(m/z 224) proved to be 9.6. This compound yields a base peak which is 9.6 times higher in the SI mode than in the EI mode. However, it should be noted that our comparison was limited to the SI and EI sources used in the present studies and may have only a qualitative meaning.

The present mass spectrometric study demonstrates that SI mass spectrometry can be useful as an alternative, or at least complementary, to conventional EI mass spectrometry. GC–SIOMS and GC–SID can be promising for trace analysis of the drug haloperidol.

4. Determination of haloperidol in serum

4.1. GC–SID

The present SIOMS studies revealed that SI gives greater output ion currents for haloperidol. Hence, the SID appears to have greater potential in the routine analysis performed in clinical laboratories, which requires sensitive, selective, rapid, positive identification and determination. From the use of the SID, two advantages may be expected: first, because of the high specificity, the possibility of interference is greatly reduced and clean-up procedures are usually unnecessary and secondly, due to the detector's increased sensitivity, a better detection capability is achieved.

Fig. 3 shows a typical SID chromatogram obtained from the analysis of a chloroform extract of blank and spiked serum samples. No concentration procedure was included. Major points of interest concern the detection limit and the presence of interfering peaks. As can be seen from Fig. 3, no interfering peaks were observed in GC profiles of serum extracts, demonstrating the specificity of the SID. After confirming the linearity of the response, the detection limit was measured for the overall method (a 10- μ l injection of the extraction solution

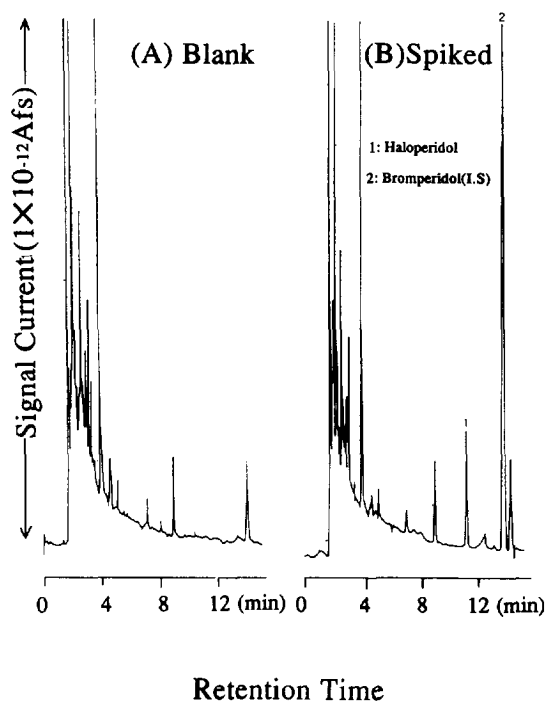


Fig. 3. SID chromatograms of an extracted blank and a spiked serum sample of haloperidol, illustrating quantitative detection limits of 1.1 ng/ml ($S/N=3$). Chromatograms of extract (injection of 10 μ l) from blank human serum (A) and from human serum spiked with 25 ng/ml haloperidol and 250 ng/ml bromperidol (B).

from the spiked serum sample of 500 μ l). The detection limit of 1.1 ng/ml is determined at a signal-to-noise ratio of three, provided that no other substance in the serum interferes with each peak.

The accuracy and precision of the assay procedure were determined from replicate analyses ($n=10$) by measuring three different plasma samples, each spiked with haloperidol. The coefficients of variation for these assays were 8.5, 1.9 and 3.0%, respectively. Absolute recoveries for haloperidol at 15 and 400 ng/ml were found to be 92.7 and 96.3%, respectively. Complete results are shown in Table 2. The absolute recovery for the internal standard, bromperidol, was found to be $100.6 \pm 2.4\%$ at 250 ng/ml. The good reproducibility of the method is partly due to the reliability of the SID and to the minimal handling of samples.

Seno et al. [3] have recently used a method similar to the above one to analyze haloperidol in whole

Table 2

Analytical results for haloperidol, determined in serum samples from replicate analyses ($n=10$) with spiked drug levels ranging from 15 to 400 ng/ml

Added (ng/ml)	Accuracy, precision and recovery		
	Found (mean±S.D.)	Recovery (%)	C.V. (%)
15.0	13.9±1.187	92.7	8.5
150.0	157.4±2.93	105	1.9
400.0	385.0±11.49	96.3	3.0

blood and urine from schizophrenic patients receiving 3-mg doses of these drugs in one day. They have encountered no difficulties with the method used in these analyses and have confirmed the validity of this method for routine analysis. The routine determination of haloperidol in serum can be reliably made at concentrations as low as 1.5 ng/ml (at a signal-to-noise ratio of three).

4.2. Comparison of SID with flame thermionic detection (FTD)

Fig. 4 shows a comparison of SID with FTD used in GC in terms of overall detection limit of haloperidol in serum. Chromatograms are shown for 10- μ l injections of a chloroform extract from a 500- μ l aliquot of the serum spiked with 100 ng/ml of haloperidol and 500 ng/ml of bromperidol (internal standard) using the same analytical procedure with SID and FTD. The FTD measurements were made under optimum conditions, with the maximum sensitivity at $5 \cdot 10^{-14}$ g/s for azobenzene (catalog specification). The SID offered a sensitivity enhancement over the well-established FTD in the detection of haloperidol of, at least, a factor of ca. 24. Furthermore, long term operation of the SID at such a high sensitivity scale as $1 \cdot 10^{-12}$ AUFS shows no serious instability.

4.3. GC-SIOMS

In cases where better specificity and sensitivity are critical, such as in forensic work, the use of capillary columns with selected ion monitoring by EI mass spectrometry may be the best method [27]. It has been the basis of many clinical studies.

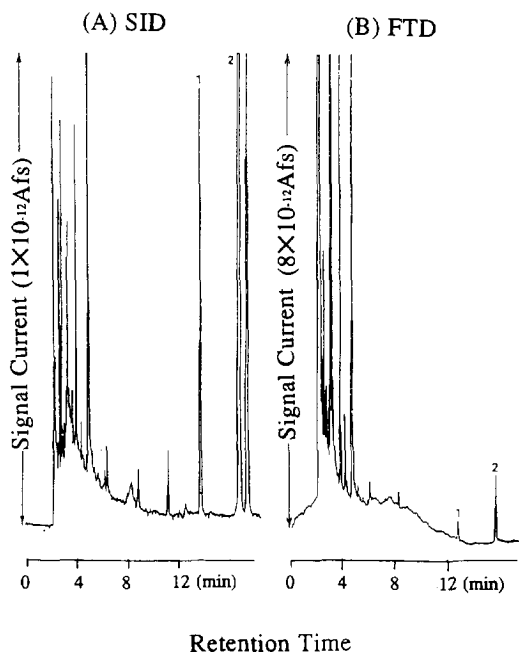


Fig. 4. Surface ionization detector (SID) gas chromatogram (A) of a serum sample supplemented with haloperidol and bromperidol (internal standard), together with a FTD chromatogram (B); 10- μ l injection of extraction solution. Peaks: 1=haloperidol (100 ng/ml), 2=bromperidol (500 ng/ml), which correspond to sample amounts of 2 and 10 ng, respectively.

When combined with GC, SIOMS also seems to be a promising method for the detection of haloperidol. Work in this direction was planned because, as a rough approximation, it could be expected that the moiety of the amine radical has the potential to be surface-ionized efficiently. The above-mentioned SIOMS studies have yielded promising results.

Fig. 5 shows a result obtained with total ion monitoring (TIM), when the mass spectrometric operation was carried out both by EI (right panel) and by SI (left panel). The sample was a 5- μ l extract solution of drug-free serum samples supplemented with haloperidol in concentrations of 10 and 1 μ g/ml, respectively. Interestingly, TIM in the SI mode shows no interference from the compounds associated with the blood, in which a large variety of normal constituents can usually give interfering peaks. The haloperidol peak of both TIMs yields an easily identified mass spectrum, which is, as expected, almost identical to that obtained from a direct introduction of the pure substance.

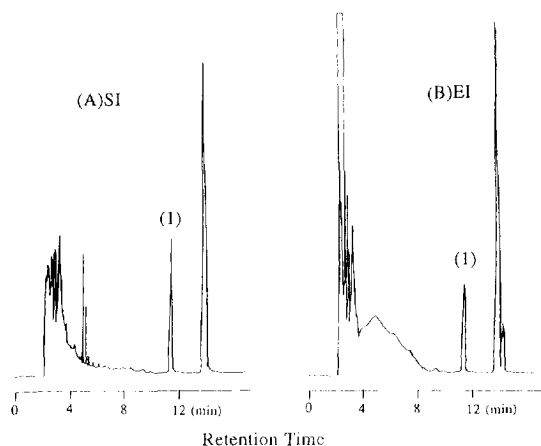


Fig. 5. Comparison of total ion chromatograms of haloperidol in a spiked serum sample obtained by (A) the SI mode and (B) the conventional EI mode. On the assumption that the extraction efficiency is 100%, the haloperidol peak of the TIM profiles in the SI mode corresponds to 10 ng, while the peak in the EI mode corresponds to 100 ng.

Comparison with the EI mode reveals that GC-SIOMS does not give rise to peak broadening, tailing and baseline drift in the TIM profiles, owing to its fast response characteristics. Thus, the SI is compatible with capillary column techniques.

Another important aspect of using the SI technique for mass spectrometry is its high sensitivity, as demonstrated by a comparison of TIM. A haloperidol concentration in the serum of 42 ng/ml (a haloperidol sample amount of 420 pg) was calculated as the detection limit at a signal-to-noise ratio of three from TIM profiles obtained with the SI. It should be noted, however, that these results are only valid for our instruments which are quite old and give only a qualitative comparison with those of SID.

The preliminary study on the accuracy and precision of this GC-SIOMS method showed that the results are comparable to those of GC-SID obtained for haloperidol. Certainly, the detection procedure (to choose the characteristic ions such as the base peak m/z 123, in light of the SI mass spectrum) by selected-ion monitoring allows the determination of much lower concentrations in serum, which is at, or below, those typically used in clinically important samples. This procedure was not performed in this study because of instrumentation limitation.

5. Conclusions

We have demonstrated the application of SIOMS to the characterization study of haloperidol as an alternative to conventional EI mass spectrometry. It has been shown, in particular, that a better idea of the possibilities and limitations could be obtained using the SI technique, which results in the production of only a few abundant specific ions. The principal points are as the following: (a) GC-SID is a valuable and important tool in haloperidol analysis, with better sensitivity than other GC methods with NPD; (b) GC-SIOMS allows identification of drugs with certainty, as a complementary method to conventional EI, and offers a reliable basis for the GC-SID method; (c) GC-SIOMS may detect a large number of drug metabolites under conditions where an extensive SI mass spectral library is established; (d) to make full use of the GC-SID advantages, an SI mass spectral library is also essential. In these respects, the GC-SID and GC-SIOMS methods associated with the SI technique can result in new opportunities in the field of pharmacology.

GC-SID can be used for a preliminary screening to detect haloperidol, using a simple one-step extraction procedure with 1 M NaOH in chloroform. This procedure has been validated in the range of 1–500 ng/ml, thus allowing the sensitive and selective analysis of drug serum levels in patients undergoing clinical treatment.

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