Journal of Chromatography, 416 (1987) 445–446
Biomedical Applications
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROMBIO. 3585

Letter to the Editor

Rationale for application of low-mass selected-ion detection in the quantitative body fluid assay of nadolol

Sir,

The gas chromatographic–mass spectrometric (GC–MS) assay for nadolol was developed in 1976 to accurately assay the levels of nadolol after a single oral administration to human subjects [1]. Within the context of the requirements of studies, our methods have provided more than 30 000 assays to human clinical groups [1–3]. The MS data were validated [1] against a fluorometric method [4] specific to the polyhydroxylated β-blocker nadolol.

When other drugs are coadministered, the specificity and accuracy of the nadolol method have been validated again. In the several instances when it was required, we did not detect any interference. Although we do not challenge our analytical systems to all possible drugs, all of the *tert.*-butylamino β-blockers cited in Professor Delbeke's letter would yield silylated derivatives that are less than 400 daltons. Nadolol is unique in that it forms a silylated derivative with a mass of 525 daltons. As a consequence, nadolol would have a longer retention time. The chromatographic conditions are either suitable to separate the analyte from other potentially interfering β-blockers or the conditions could be readily adjusted. As for the other drugs that potentially have electron-impact mass spectra with a base ion of m/z 86, we could demonstrate non-inteference on a need basis, if required. As for specificity at low masses, we have shown in various publications [1–3] the non-interference of coextracted plasma components in the measurement of nadolol.

Delbeke and Debackere [5] recommend the use of a trifluoroacetyl derivative as a viable derivatization alternative. Indeed in our original publication [1] we investigated its use and found considerable difficulty in making a pure derivative. At that time Claeys et al. [6] reported problems in using these powerful acetylating agents. After review of the Garteiz and Walle publication [7], we concluded that trifluoroacetylation would yield an m/z 322 ion and the generic β-blocker side-chain m/z 266 ion. Trifluoroacetylation would obviate the use of the deuterated isotopomer as an internal reference [2, 3] nor would it allow performing the coadministration study [2]. Carlin et al. [8] determined timolol and showed excellent results using the m/z 86 ion. The abundance of the m/z 266 ion

0378-4347/87/$03.50

as a percentage of the total ionization would be significantly less than 40% as judged from the spectra reported by Garteiz and Walle [7].

To summarize, the nadolol method [3] is specific, sensitive and accurate because it incorporates selective extraction, GC separation and coelution with its deuterated internal reference standard.

Perhaps a more important aspect of our work is to reinforce the concept that where judiciously applied, quantitative measurements of low-mass ions can be a very powerful tool. A great variety of instruments are capable of producing sensitivity in the low mass range. The separation power of capillary GC can produce the selectivity required. Many mass spectrometers tend to discriminate against higher-mass ions. In a recent note, we described several potential instances where the electron-impact ionization process was redirected from a variety of fragment ions, each less than 10% of the total ionization, to one of 40% of the total ionization for diethylaminoethyl esters [9]. In that note we suggested the potential use of ion directing derivatives in the enhancement of sensitivity. When compared to the alternatives of the application of quantitative chemical ionization, the use of inexpensive electron-impact mass-selective detectors appear very attractive.

Squibb Institute for Medical Research,
P.O. Box 191,
New Brunswick, NJ 08903 (U.S.A.)

ALLEN I. COHEN*
MOHAMMED JEMAL
EUGENE IVASHKIV
MICHAEL RIBICK

1 P.T. Funke, M.F. Malley, E. Ivashkiv and A.I. Cohen, J. Pharm. Sci., 67 (1978) 653.
2 A.I. Cohen, R.G. Devlin, E. Ivashkiv, P.T. Funke and T. McCormick, J. Pharm. Sci., 73 (1984) 1571.
3 M. Ribick, E. Ivashkiv, M. Jemal and A.I. Cohen, J. Chromatogr, 381 (1986) 419.
4 E. Ivashkiv, J. Pharm. Sci., 66 (1977) 1168.
5 F.T. Delbeke and M. Debackere, J. Chromatogr., 416 (1987) 443.
6 M. Claeys, G. Muscettola and S.P. Markey, Biomed. Mass Spectrom., 3 (1976) 110.
7 D.A. Garteiz and T. Walle, J. Pharm. Sci., 61 (1972) 1728.
8 J.R. Carlin, R.W. Walker, R.O. Davies, R.T. Ferguson and W.J.A. Vandenheuvel, J. Pharm. Sci., 69 (1980) 1111.
9 A.I. Cohen and M. Jemal, Anal. Chem., 57 (1985) 2151.

(Received January 5th, 1987)