Journal of Chromatography, 603 (1992) 294–297
Elsevier Science Publishers B.V., Amsterdam

CHROM. 24 164

Short Communication

Gas chromatographic–mass spectrometric detection of trace amounts of organic compounds in the intravenous solution Infusio Darrowi

Jan Lesko and Tibor Jakubik

Laboratory for Mass Spectrometry, Faculty of Chemical Technology, Slovak Technical University, Radlinskeho 9, 812 37 Bratislava (Czechoslovakia)

Anna Michalkova

State Institute for Drugs Control, Kvetna 11, 825 08 Bratislava (Czechoslovakia)

(First received November 4th, 1991; revised manuscript received March 3rd, 1992)

ABSTRACT

A gas chromatographic–mass spectrometric procedure was employed to confirm the presence of trace amounts of organic compounds in the intravenous solution Infusio Darrowi. Organic contaminants in the solution analysed were concentrated by microextraction with *n*-pentane. The main compounds detected were 2,6-di-*tert.*-butyl-4-methylphenol, 2,6-di-*tert.*-butyl-4-ethylphenol, 2,6-di-*tert.*-butyl-4-methoxyphenol, benzothiazole, isomeric C_9 alkyl phenols and di(*n*-butyl) phthalate. These impurities were leached from rubber stoppers during their sterilization into the intravenous solution at levels ranging *ca.* from $5 \cdot 10^{-6}$ to $5 \cdot 10^{-8}$ g/l.

INTRODUCTION

Plastics are widely used in the manufacture of drugs packaging and medical devices. The most common plasticizers are phthalate esters, which may migrate from plastic devices and containers into contacting media. The leachability of plasticizers [particularly of di-(2-ethylhexyl) phthalate] from plastic devices into blood, blood products, haemodialysis fluids and intravenous solutions has been extensively studied, using gas chromatography, gas chromatography–mass spectrometry (GC–MS) [1–10] and high-performance liquid chromatography [11].

The objective of this study was to examine the sources of contamination of the intravenous solution Infusio Darrowi, which had been prepared under standard conditions in a laboratory. The impurities in this intravenous solution and in the chemicals used for its preparation were determined by GC–MS analyses of the particular *n*-pentane extracts.

Correspondence to: Dr. J. Lesko, Laboratory for Mass Spectrometry, Faculty of Chemical Technology, Slovak Technical University, Radlinskeho 9, 812 37 Bratislava, Czechoslovakia.

0021-9673/92/$05.00

EXPERIMENTAL

Chemicals

The following chemicals were used: *n*-pentane of spectroscopic grade (Merck, Darmstadt, Germany), 1-chlorooctane (Aldrich-Chemie, Steinheim, Germany), sodium chloride and potassium chloride of the quality complying with the requirements of the present Czechoslovak Pharmacopoeia (Lachema, Brno, Czechoslovakia) and 1 *M* sodium lactate injection (Biotika, Slovenska Lupca, Czechoslovakia).

The final product Infusio Darrowi (sodium chloride 4.00 g, potassium chloride 2.67 g, 1 *M* sodium lactate injection 53.00 ml, redistilled water to 1000.00 ml), was prepared in the Microbiological Department of the District Laboratory for Drugs Control of Western Slovakia (Bratislava, Czechoslovakia) in accordance with the requirements of the Czechoslovak Pharmacopoeia.

Extraction procedure

In this study, experience with microextraction [12–15] for the concentration of trace impurities was used. Organic contaminants in the samples were concentrated by a single-stage microextraction with *n*-pentane [12]. The sodium lactate injection and Infusio Darrowi prior to and after autoclaving (121°C for 20 min) were extracted directly. Sodium chloride and potassium chloride were extracted from their solutions in redistilled water (20 g/l). The solutions were cooled to 5°C prior to the extraction, the internal standard 1-chlorooctane (10^{-5} g/l) was added and the solutions were extracted with *n*-pentane (0.5 ml/l). An aliquot of the extract was used directly for GC–MS analysis.

GC–MS conditions

GC–MS measurements were made with a Kratos Analytical (Manchester, UK) MS 25 RFA mass spectrometer equipped with a Carlo Erba (Milan, Italy) Model 5160 gas chromatograph. A Chrompack (Middelburg, Netherland) fused-silica capillary GC column (25 m × 0.32 mm I.D.) with a CP-Sil 5 CB coating (0.12 μm) was used. Helium was used as the carrier gas. The injector temperature was 250°C. The GC oven temperature was programmed as follows: 1 min at 40°C, increased at 4°C/min to 100°C, then at 10°C/min to 240°C. For MS, electron impact ionization was used, the source temperature was 200°C, the electron energy was 70 eV and the scan speed was 0.6 s per decade.

RESULTS AND DISCUSSION

GC separations of organic impurities in Infusio Darrowi prior to and after sterilization are shown in Fig. 1a and b, respectively. Organic compounds were identified according to their mass spectra by a library search. A comparison of Fig. 1a and b reveals that some of these compounds were detected only in the sterilized solution or that their concentration was increased on sterilization.

As the intravenous solutions are sterilized in glass bottles, the only possible source of contamination with leached organic compounds during the sterilization procedure is the black rubber stoppers. Derivatives of di-*tert.*-butylphenols are known to be used as antioxidants and phthalate esters as plasticizers in the chemical industry. The source of benzothiazole (Fig. 2a) is probably 2-mercaptobenzothiazole, widely applied as a rubber accelerator. We did not succeed in identifying the compound with scan number 830 (Fig. 1b, mass spectrum in Fig. 2b). The commercially available sodium lactate injection used contained the same organic contaminants as the final Infusio Darrowi, but their levels were lower.

The main organic impurities in the potassium chloride samples, detected later also in the final intravenous solution, were C_9-alkylphenols. Their content varied from batch to batch and obviously depended on the packaging material and the storage of the product (in some batches phenol and cresol were also found).

The amount of organic contaminants in the sodium chloride samples was negligible. Except for di(*n*-butyl) phthalate, no other impurities were detected. Traces of di(*n*-butyl)phthalate were the only contamination found in the extractant *n*-pentane and the redistilled water, used for the preparation of all the solutions analysed.

The semi-quantitative determination of levels of organic impurities was based on calculations using the ratio of the peak areas of these compounds to that of the internal standard. The concentrations of organic contaminants in the final intravenous solution determined this way ranged from $5 \cdot 10^{-6}$ to $5 \cdot 10^{-8}$ g/l.

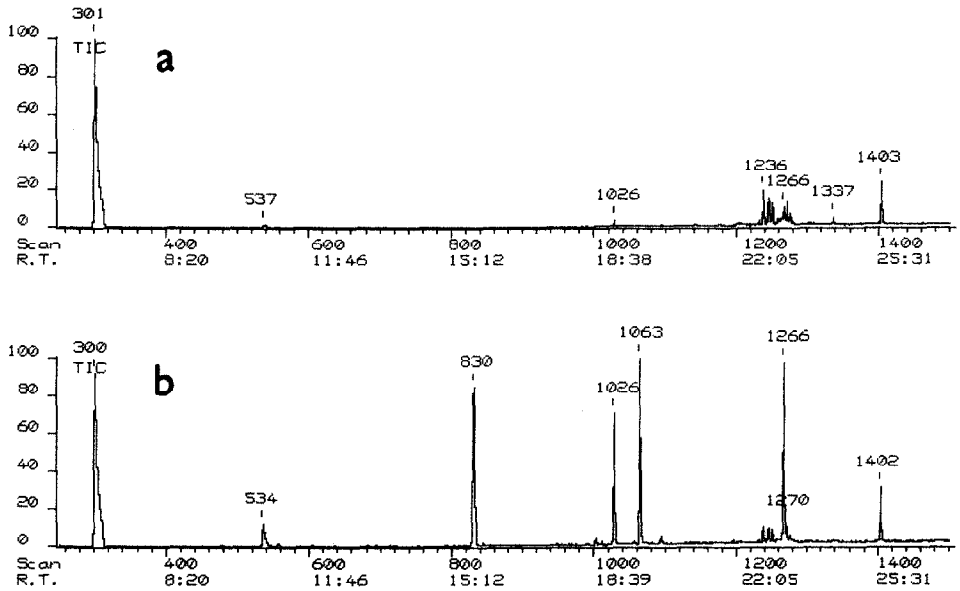

Fig. 1. Chromatogram of the *n*-pentane extract of the intravenous solution Infusio Darrowi (a) prior to and (b) after sterilization. Scan numbers: (a) 301 = 1-chlorooctane (internal standard), 537 = benzothiazole, 1026 = 2,6-di-*tert.*-butyl-4-methoxyphenol, 1236–1259 = isomeric C_9-alkylphenols, 1403 = di(*n*-butyl) phthalate; (b) 300 = 1-chlorooctane (internal standard), 534 = benzothiazole, 830 = unidentified, 1026 = 2,6-di-*tert.*-butyl-4-methoxyphenol, 1063 = 2,6-di-*tert.*-butyl-4-methylphenol, 1237–1244 = isomeric C_9-alkylphenols, 1266 = 2,6-di-*tert.*-butyl-4-ethylphenol, 1402 = di(*n*-butyl) phthalate. R.T. = Retention time in min:s.

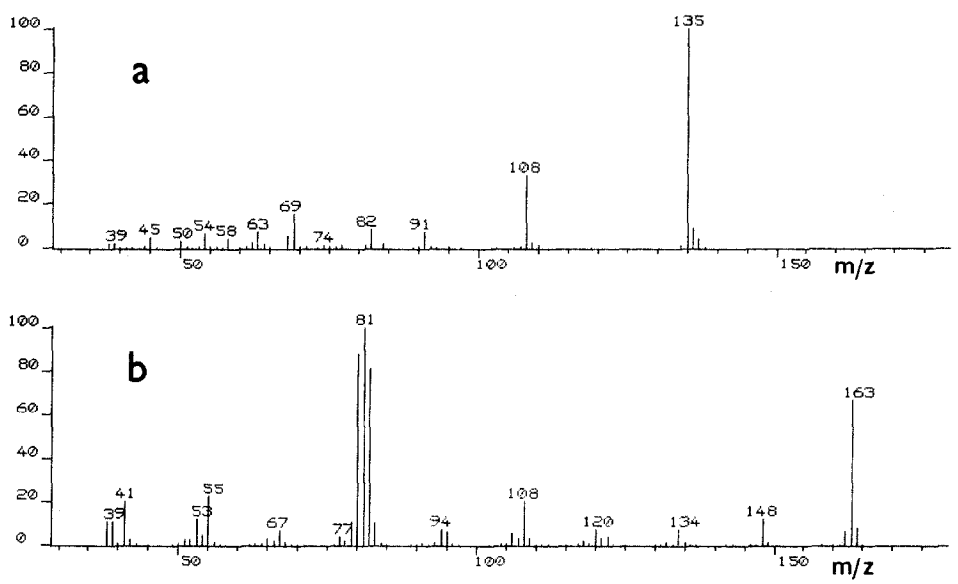

Fig. 2. Electron impact mass spectra obtained by GC–MS analysis of a Infusio Darrowi sample after sterilization. (a) Scan 534, benzothiazole; (b) scan 830, unidentified compound.

CONCLUSIONS

A simple and rapid method was developed for the preconcentration and identification of organic contaminants in the intravenous solution Infusio Darrowi and in chemicals used for its preparation. The microextraction and consecutive GC–MS analysis can be employed as a sensitive and reliable control method for the detection of trace amounts of organic impurities. Rubber stoppers proved to be the main source of contamination with organic compounds leached into intravenous solutions during their sterilization.

REFERENCES

1 L. S. Hillman, S. L. Goodwin and W. R. Sherman, *J. Med.*, 292 (1975) 381.
2 N. P. H. Ching, G. N. Jham, Ch. Subbarayan, D. V. Bowen, A. L. C. Smit, Jr., C. E. Grossi, R. G. Hicks, F. H. Field and T. F. Nealon, Jr., *J. Chromatogr.*, 222 (1981) 171.
3 A. Arbin, S. Jacobsson, K. Hänninen, A. Hagman and J. Östelius, *Int. J. Pharm.*, 28 (1986) 211.
4 K. Ono, R. Tatsukawa and T. Wakimoto, *J. Am. Med. Assoc.*, 234 (1975) 948.
5 P. O. Sjöberg, U. G. Bodesson, E. G. Sedin and J. P. Gustafsson, *Transfusion*, 25 (1985) 424.
6 T. P. Gibson, W. A. Briggs and B. J. Boone, *J. Lab. Clin. Med.*, (1976) 519.
7 L. M. Lewis, T. W. Flechtner, J. Kerkay, K. H. Pearson and S. Nakamoto, *Clin. Chem.*, 24 (1978) 741.
8 L. Nässberger, A. Arbin and J. Östelius, *Nephron*, 45 (1987) 286.
9 B. Kakac, M. Sarsunova, Z. Perina, A. Michalkova, J. Hrivnak and H. Berankova, *Pharmazie*, 44 (1989) 31.
10 A. Arbin and J. Östelius, *J. Chromatogr.*, 193 (1980) 405.
11 R. S. Labow and M. Tocchi, *J. Toxicol. Environ. Health*, 19 (1986) 591.
12 J. Hrivnak, *Anal. Chem.*, 57 (1985) 2159.
13 D. A. J. Murray, *J. Chromatogr.*, 177 (1979) 135.
14 D. A. J. Murray and L. W. Lockhart, *J. Chromatogr.*, 212 (1981) 305.
15 J. Ilavsky, Thesis, Slovak Technical University, Bratislava, 1989.