A convenient online desalination tube coupled with mass spectrometry for the direct detection of iodinated contrast media in untreated human spent hemodialysates.

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論文題目

A convenient online desalination tube coupled with mass spectrometry for the direct detection of iodinated contrast media in untreated human spent hemodialysates.

（便利なオンライン脱塩チューブおよび質量分析を用いた未処理ヒト透析排液からのヨード系造影剤の直接検出）

論文の内容の要旨

[Introduction]

Mass spectrometry (MS) analysis using direct infusion of biological fluids is often problematic due to high salts and nonvolatile solutes/buffers. The presence of excess salts and nonvolatile solutes/buffers in biofluids is not desired to ensure a stable electrospray ionization (ESI)-MS analysis. However, some bio-fluids (cerebrospinal fluids) are salty, while other biofluids (proteins/protein mixtures) need nonvolatile salts/buffers and solubilizing agents (detergents) to preserve their stability and conformational integrity. Therefore, direct analysis of untreated biofluids by MS represents a considerable challenge.

Iodinated contrast media (ICM) are widely used for diagnostic imaging, but concerns about their potential toxicities have also increased with their widespread use. Therefore, the detection of ICM in spent hemodialysates is important for assessing the patient's treatment and other complications in acute kidney injury (AKI) patients receiving continuous hemodiafiltration (CHDF). However, existing methods for online desalting and direct infusion of biological samples without chromatographic separation often suffer from ion suppression. To overcome this, integrating an online desalination tube before MS enables direct injection of untreated, salty spent hemodialysates. This approach not only detects ICM and metabolites but also monitors the changes of ICM with time. It also successfully resolves the issue of ion suppression, bringing it closer to its use in clinical practice.

[Patients and Methods]

This study was approved by the ethics committee of Hamamatsu University School of Medicine, Japan (ethical approval number:19-169), and written informed consent was obtained from the patients. The desalination tubes were purchased from MS-Solutions (Tokyo, Japan). Spent hemodialysates were obtained from three patients admitted to the intensive care unit of Hamamatsu University Hospital, Japan. Firstly, spent hemodialysates of one patient were injected directly into the ESI source equipped with a quadrupole time-of-flight mass spectrometer (Q-TOF MS) connected to an online desalination tube for ICM and metabolites screening. Thereafter, spent hemodialysates

of two patients were injected directly into the ESI source equipped with a triple quadrupole MS (TQ-MS) connected to that online desalination tube to confirm the detection of ICM.

[Results]

We detected iohexol (an ICM) in the untreated spent hemodialysates of the patient received for computed tomography using Q-TOF MS. Using multiple reaction monitoring (MRM) analysis, we have confirmed the detection of ICM in the untreated spent hemodialysates of the patients received for coronary angiography before starting CHDF. MRM profiling was evaluated based on the relative intensities of specific product ion transition (*m/z* 807.9>588.8) confirmed in the TQ-MS. We observed approximately 178 times higher signal intensity and 8 times improved signal-to-noise ratio (S/N) for ioversol (an ICM) when using the desalination tube compared to data obtained without it. This method detected ioversol at the lowest known concentration (0.1 ng/mL) in spent hemodialysates or methanol which facilitated the detection of ioversol in the collected samples. By applying our method, we observed higher ioversol signal intensity of patient #2 at 1h and then decreased the signal intensity at 2h, 4h, 6h, and 24h. In contrast, Patient #3 had the higher ioversol signal intensity at the beginning (0h) followed by a decrease after 0.5h, 1h, 2h, 4h, 6h, and 24h of starting CHDF. Throughout the observation period, patient #3 consistently had higher ioversol signal intensity compared to patient #2.

[Discussion]

In this study, we connected the online desalination tube before ESI-MS that enabled direct injection of untreated salty spent hemodialysates into MS. The desalination tube purifies the spent hemodialysates based on the ion-exchange technique, consequently resolving issues such as excess inorganic salts, nonvolatile solutes/buffers, and other impurities. It acts as a contaminant remover that causes diffusion in the physical spaces within the tube or adsorption on ion-exchange resin depending on the analytes. This approach showed stable and higher signal sensitivity for contrast agents and other endogenous metabolites simultaneously due to the online desalting capability. Unlike, the conventional workflows that require sample extraction and chromatographic separation, we successfully detected the iohexol and ioversol in untreated spent hemodialysates without these additional steps. The use of the online desalination tube reduced the laborious work and sample clean-up time, resulting in faster analysis. This configuration is also beneficial for overcoming the ion suppression effect**,** which results in increased signal intensity and improved spectral S/N. It enhances the signal intensity and improves the S/N for ioversol (*m/z* 807.9>588.8) by approximately 178 times and 8 times, respectively. The increased ioversol signal intensity in patient #3 compared to

patient #2 was caused by getting higher ioversol doses prior to CHDF.

[Conclusion]

The online desalination tube coupled with MS showed the capability of direct detection of iohexol and ioversol in untreated salty spent hemodialysates with high sensitivity. It also showed the ability to track the changes of ioversol in spent hemodialysates of AKI patients.