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Dialyzability of Surfactants Commonly Used in Pesticide Formulations

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Abstract

Objective: This study aimed to determine the dialyzability of common pesticide surfactants.

Methods: Hemodialysis and hemoperfusion were performed for three surfactants-sodium dodecylbenzenesulfonate, lignosulfonic acid sodium, and naphthalenesulfonic acid polymer with formaldehyde-with buffer solutions (2 L) containing 0.2% surfactant with or without bovine serum albumin (3.0 g/dL).

Results: The dialyzability of sodium dodecylbenzenesulfonate during hemodialysis was high and increased with ultrafiltration. The final reduction rates of naphthalene sulfonic acid polymer with formaldehyde and sodium dodecylbenzenesulfonate in bovine serum albumin were higher for hemoperfusion (25.8% and 26.8%, respectively) than for hemodialysis (8.2% and 0%, respectively). In contrast, the final reduction rate of lignosulfonic acid sodium in bovine serum albumin was higher for hemodialysis (37.5%) than for hemoperfusion (13.2%).

Conclusion: Our results suggest that extracorporeal elimination may be an effective treatment modality in patients who ingested surfactant mixed pesticides. However, the dialysis method looks likely to be tailored to each surfactant, based on its dialyzability.

Keywords: Dialysis efficiency; Hemodialysis; Direct hemoperfusion; Surfactant

Introduction

Patients who ingest low-toxicity pesticides sometimes suffer from severe toxicity effects such as respiratory distress, metabolic acidosis, tachycardia, renal failure, and electrolyte imbalances [1,2]. We previously reported that pesticide surfactants significantly damage cell membranes and disturb cellular metabolic activity, mitochondrial activity, and protein synthesis *in vitro* [3]. This might be caused by surfactants commonly included as emulsifiers or dispersants.

Although multiple reports showed the effectiveness of intravenous lipid emulsion for surfactant-induced hypotension and arrhythmia in humans, it is ineffective against loss of consciousness and respiratory distress [4]. Extracorporeal elimination of toxic substances has saved lives [5], but its efficacy depends on two major factors: the characteristics of the toxin and the method for extracorporeal elimination [6]. However, data on extracorporeal removal of surfactants are limited.

The purpose of this study was to evaluate the dialyzability of common pesticide surfactants using hemodialysis (HD) and hemoperfusion (HP).

Materials and methods

We chose three common pesticide surfactants having specific wavelengths of maximum absorbance (λmax) >250 nm: sodium dodecylbenzenesulfonate (DBSA, 260 nm, CAS # 25155-30-0; Sigma-Aldrich), lignosulfonic acid sodium (LSA, 280 nm, CAS # 8061-51-6; Sigma-Aldrich), and naphthalenesulfonic acid polymer with formaldehyde (NSPF, 287 nm, CAS # 9084-06-4; Wako Pure Chemicals). The limit of detection of the surfactants was about 0.00002–0.0001% (w/v). A two-liter solution of 0.2% surfactant in 0.1 M sodium bicarbonate, pH 7.4, with or without BSA (3.0 g/dL) was made.

The effect of protein binding on dialyzability was evaluated using bovine serum albumin (BSA). To separate the surfactants from BSA, 100 mg of hydrophobic resin C18 (Alltech) was loaded on a Spin-X filter (Corning) and equilibrated with acetonitrile and water. HP or HD samples (20-100 µL) were loaded on the filter and centrifuged for 1 min at 500 ×g. The filtrate was reloaded onto the filter and the process was repeated twice. The filter was washed thrice with 1 mL of water followed by centrifugation at 2000 ×g for 1 min. The surfactant was eluted twice with 0.5 mL of 30% acetonitrile while BSA was still bound to the resin. HD and HP were performed using the Gambro AK 200ULTRA S system. The dialyzer was a Polyflux 170H (Polyamix membrane; Gambro Dialysatoren Hechingen, Germany). The HP cartridge was an Adsorba 300 C (Gambro Dialysatoren) that had polypropylene housing material, activated charcoal with cellulose coating, and a 300-m^2 surface area.

During dialysis, the sample flow rate was kept at 250 mL/min. The dialysate flow rate was 500 mL/min. The HD setting was changed to an ultrafiltration rate of 500 g/h 60 min after initiation of dialysis. Surfactant solutions were sampled at the inlet (artery line when applied

to a patient) and outlet (venous lines when applied to a patient) of the dialyzer and cartridge at 0, 5, 30, 60, 90, and 120 min of dialysis. The samples were stored at 4 °C until analysis. The experiment was carried out three times for each of HD and HP.

All data are presented as the mean ± standard deviation from three independent experiments. A linear mixed model was used for detecting associations between the reduction rates or concentrations in the containers and dialysis type or duration. The correlation structure for adjusting repeated measurements of each variable was selected using the Akaike information criterion. The final surfactant reduction rate was calculated as follows:

Final reduction rate = [[(Concentration at time 0)-(final concentration after 120 min of dialysis)]/(Concentration at time 0)] × 100

A p-value <0.05 was considered significant. All data were analyzed using IBM SPSS version 17.0 for Windows, and the R program (v3.1.2) was used for plotting data.

Results

BSA significantly lowered the reduction rate of NSPF (effect of BSA coefficient: -3.558; Figure 1). The final reduction rate of NSPF was 67.7%, 40.3%, 25.8%, and 8.2% for HD without BSA, HP without BSA, HP with BSA, and HD with BSA, respectively (Figure 2).

The effect of BSA on the DBSA reduction rate was negligible for both HD and HP (β=-13.563, p<0.001). The reduction rate increased with ultrafiltration (β=10.502, p<0.001; Figure 1). The final reduction rates of DBSA were 93.9%, 80.0%, 26.8%, and 0% for HD without BSA, HP without BSA, HP with BSA, and HD with BSA, respectively.

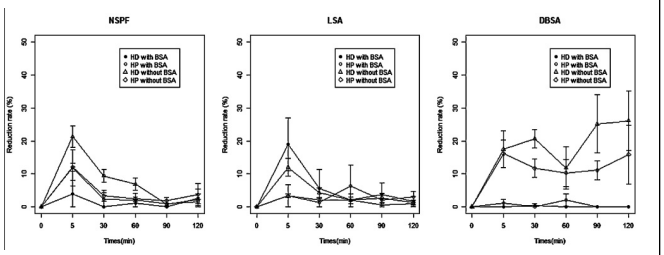

Figure 1: Changes in reduction rates during dialysis. NSPF: The reduction rate was greatest at 5 min after the initiation of dialysis and decrease as the dialysis progressed The reduction rate was significantly lower when the NSPF was existed together with BSA than it existed alone without BSA (effect of BSA coefficient: -3.558). It decreased as the time of dialysis passed, regardless of both the existence of BSA and the type of dialysis (p<0.001). DBSA: The reduction rate of DBSA was negligible in both HD and HP, when NSPF existed with BSA (β=-13.563, p<0.001). It was greatest at 120 min when an ultrafiltration procedure was applied. (β=10.502, p<0.001). LSA: The reduction rate was between 0.6 and 6.3% when the LSA existed with BSA, in both HD and HP. It was greater in the first 5 min (β=9.417, p<0.001), and there was no specific change during the later dialysis period. (BSA effect p=0.295, HD or HP p=0.063).

The reduction rates of LSA with BSA were between 0.6% and 6.3% for HD and HP. We observed peak reduction rate during the first 5 min (β=9.417, p<0.001), with no specific change afterwards (BSA effect: p=0.295 for HD and p=0.063 for HP; Figure 1). The final reduction rates of LSA were 39.9%, 37.5%, 30.8%, and 13.2% for HD without BSA, HD with BSA, HP without BSA, and HP with BSA, respectively.

Discussion and conclusion

Substantial evidence from *in vitro* experiments [7-9] and *in vivo* observations [1,9,10] supports the possible toxicity of surfactants to humans. However, there is no direct evidence of surfactant-mediated toxicity in humans, even in patients who ingested undiluted pesticides containing surfactants. One of the reasons for this uncertainty is the lack of toxicokinetic data for each surfactant because of the technical difficulty in measuring surfactants in plasma or serum. Even with this limitation, clinical toxicologists generally perform extracorporeal elimination as an early treatment modality in patients with critical toxic symptoms after ingestion of a large amount of undiluted pesticides [11-13]. Against this background, we designed this pilot study prior to a large-scale study in humans, which will have to be performed after technical development of a technique for measuring surfactant in plasma or serum.

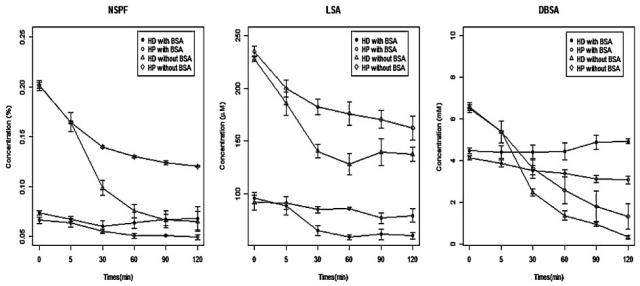

Figure 2: Changes in the surfactant concentrations in the containers during dialysis. Dialysis was started using the same concentration of 0.2% (w/v) for all surfactants. The unit was converted to μM and mM for LSA and DBSA, respectively, but not for NSPF, which has an unknown molecular weight. Note the lower decreases of the surfactant concentrations in the presence of BSA. The final reduction rate of NSPF concentration was 67.7% for HD without BSA, 40.3% for HP without BSA, 25.8% for HP with BSA, and 8.2% for HD with BSA in order. The final reduction rate of DBSA concentration was 93.9% for HD without BSA, 80.0% for HP without BSA, 26.8% for HP with BSA, and 0% for HD with BSA in order. The final reduction rate of LSA concentration was 39.9% for HD without BSA, 37.5% for HD with BSA, 30.8% for HP without BSA, and 13.2% for HP with BSA in order.

We measured the surfactant concentration based on absorbance. Three surfactants showed specific spectra that allowed differentiating the surfactants from BSA, salts, etc. The surfactants were separated from BSA by solid-phase extraction using a C18 hydrophobic sorbent. DBSA, a negatively charged surfactant, was highly dialyzable with HD and even more so when combined with ultrafiltration. Its reduction rate with HP remained above 10% during the entire 120 min of dialysis. In comparison, the dialyzability of both NSPF and LSA (also negatively charged) decreased over time. These findings suggest that the surfactant's charge is not a major factor for dialyzability. However, BSA dramatically decreased the dialyzability of all three surfactants

(Figure 2). When BSA was added to NSPF and DBSA, the reduction rate was greater when using HP (25.8% and 26.8%, respectively) than with HD (8.2% and 0%, respectively). In contrast, when BSA was present in LSA, the reduction rate was greater when using HD (30%) than when using HP (7.2%). This implies that the effectiveness of HP and HD depends on the type of surfactant.

Our study had some limitations. Only few surfactants were tested. The effect of protein binding on the dialyzability was assessed only with BSA. Therefore, the experimental setup presented a rather artificial system, which may be difficult to translate to clinical practice. Even with these limitations, our results suggest that extracorporeal elimination may be an effective treatment modality in patients who ingested surfactant mixed pesticides. The dialysis method looks likely to be tailored to each surfactant, based on its dialyzability.

Disclosure

The authors declare no conflicts of interest, and the authors alone are responsible for the content and writing of the article. We thank KB Lee of the Korea Basic Science Institute for technical support. This work was carried out with the support of the Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ01083201), Rural Development Administration, Republic of Korea.

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