Pharmacokinetics of Sodium Thiosulfate in Guinea Pig Perilymph Following Middle Ear Application

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INTRODUCTION

Objectives: To study the pharmacokinetics of sodium thiosulfate in the inner ear perilymph of guinea pigs using high pressure liquid chromatography.

Study Design: Basic science laboratory research.

Methods: Twenty guinea pig ears were split into two groups and administered sodium thiosulfate to the middle ear at a concentration of 250 mg/mL or 50 mg/mL for 30 minutes. Perilymph samples were then obtained serially through the round window over 6 hours. Sodium thiosulfate concentrations were obtained using high pressure liquid chromatography.

Results: The 250 mg/mL group had an initial perilymph concentration of 7.27 mg/mL (±0.83) and decreased to 0.94 mg/mL (±0.03) over 6 hours. The 50 mg/mL group had an initial concentration of 1.63 mg/mL (±0.17) and was undetectable after 1 hour.

Conclusions: The results of this study show that sodium thiosulfate is capable of diffusing through the round window and into the inner ear perilymph. This has a potential application as a localized therapy in the prevention of cisplatin-induced ototoxicity.

METHODS AND MATERIALS

Animal Preparation

10 retired breeder Hartley albino guinea pigs
Each ear randomized to either 50 or 250 mg/mL STS (Figure 1)
Each guinea pig was endotracheally intubated and placed under general anesthesia using inhaled isoflurane
All animals were euthanized after all samples obtained with intraperitoneal pentobarbital
Approved by SUNY Upstate’s Institutional Care and Use Committee

Surgical Technique

1% lidocaine with 1:100,000 epinephrine injected postauricularly
Postauricular incision extending to neck
Soft tissue elevated off bone
Middle ear bulla entered with a cutting burr
Vertical facial nerve drilled away to expose round window
Procedure repeated on contralateral ear
STS placed in middle ear space for 30 min
Middle ear space suctioned and irrigated
2 μL of perilymph aspirated through the round window using a 10 μL Hamilton syringe
Serial perilymph aspirations performed at 0, 30, 60, 180, and 360 min

High Pressure Liquid Chromatography (HPLC)

LC-20AT with a SPD-M20A UV-Vis detector (Shimadzu, Kyoto, Japan) was used with a LiChrospher® RP-select B LiChroCART® 250-4 anion exchange column (EMD Millipore Corp, Darmstadt, Germany)
Sample preparation (Togawa et al. 1992)
2 μL samples diluted in 8 μL of pure water
10 μL of 5mM KCl-HCl buffer added
Mixture allowed to sit for 60 min in dark
10 μL of 0.05M KCl-HCl buffer added
10 μL submitted to HPLC system using mobile phase of 40% acetonitrile and 60% 36mM succinate (pH 5.0) with flow rate of 1.0 mL/min
Linear standard curve calibrated by testing serial dilutions of STS
Height of STS signal used to determine sample concentration
STS concentration <0.9 mg/mL unable to be detected

RESULTS

Table 1. Pharmacokinetic profile of intratympanic STS in guinea pigs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>STS 250 mg/mL</th>
<th>STS 50 mg/mL</th>
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</thead>
<tbody>
<tr>
<td>Cmax (mg/mL)</td>
<td>7.27 ± 0.83</td>
<td>1.63 ± 0.17</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AUC (mg·hr/mL)</td>
<td>13.46</td>
<td>1.21</td>
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<tr>
<td>T½ (hr)</td>
<td>0.74</td>
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</tbody>
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Figure 1. Flowchart of STS randomization and sampling

Intratympanic STS
N = 20 ears (10 guinea pigs)

Group 1: 50 mg/mL STS
N = 10 guinea pigs ears
Perilymph sampled at 0, 30, 60, 180, and 360 min

Group 2: 250 mg/mL STS
N = 10 guinea pigs ears
Perilymph sampled at 0, 30, 60, 180, and 360 min

DISCUSSION

• Many agents have been shown to cross the round window membrane (RWM) including gentamicin, lidocaine, steroids, and toxins

CONCLUSIONS

• This study shows that STS has the potential to be a local therapy in the prevention of cisplatin-induced ototoxicity

REFERENCES

8. Wang J, Lloyd Eveslage ME, Fedorowicz GM, et al. Use of a UV-Vis detector for HPLC is less sensitive than a fluorescent detector

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