METHODS OF OTOPROTECTION AGAINST PLATINUM-BASED ANTINEOPLASTIC AGENTS

FIELD OF THE INVENTION

The present invention provides methods of otoprotection against platinum-based antineoplastic agents.

BACKGROUND

Platinum-based antineoplastic agents (e.g., cisplatin) are chemotherapeutic agents widely used to treat cancers and tumors. These agents are toxic and are known to induce hearing loss both in human and animal models. Thus, patients undergoing chemotherapy with platinum-based antineoplastic agents can suffer from hearing loss. There is a need for otoprotective compositions and methods to prevent or mitigate hearing loss associated with chemotherapeutic regimens including platinum-based antineoplastic agents.

SUMMARY ~~OF THE INVENTION~~

In general, the ~~invention~~ disclosure provides methods for mitigating platinum-induced ototoxicity in a subject in need thereof. The method involves administering to the subject an effective amount of a thiosulfate salt.

In some ~~embodiment~~examples, the subject was administered a platinum-based neoplastic agent not more than 7 hours prior administering the thiosulfate salt or is scheduled to be administered a platinum-based antineoplastic agent within 4 hours. In certain ~~embodiment~~examples, the subject was administered a platinum-based neoplastic agent not more than 7 hours prior administering the thiosulfate salt. In particular ~~embodiment~~examples, the subject is scheduled to be administered a platinum-based antineoplastic agent within 4.5 hours. In further ~~embodiment~~examples, the subject was administered a platinum-based neoplastic agent not more than 2.5 hours prior to administering the thiosulfate salt. In yet further ~~embodiment~~examples, the subject was administered a platinum-based neoplastic agent not more than 1 hour prior to administering the thiosulfate salt.

In some ~~embodiment~~examples, administration of an effective amount of a thiosulfate salt to the subject produces a plasma thiosulfate C_{max} that is 30 μM or less at the time of administration a platinum-based antineoplastic agent. In certain ~~embodiment~~examples, administration of an effective amount of a thiosulfate salt to the subject produces a cochlear thiosulfate C_{max} is at least 30 times greater than a cochlear C_{max} of the platinum-based antineoplastic agent. The cochlear platinum concentrations and the cochlear C_{max} are typically modeled by a pharmacokinetic simulation of intravenous infusion in a two-compartment model. For example, the pharmacokinetic simulation may be conducted using WinNonlin (Phoenix 64) PK simulation model 9 (IV infusion, 2 compartment).

In still further ~~embodiment~~examples, the thiosulfate salt is administered auricularly. In certain ~~embodiment~~examples, the thiosulfate salt is administered intratympanically, transtympanically, or by inner ear injection. In particular ~~embodiment~~examples, the thiosulfate salt is administered transtympanically or by inner ear injection.

In some ~~embodiment~~examples, the method further includes administering the platinum-based antineoplastic agent.

In certain ~~embodiment~~examples, the thiosulfate salt is an alkaline thiosulfate salt, ammonium thiosulfate salt, or a solvate thereof. In further ~~embodiment~~examples, the effective amount of a thiosulfate salt is administered as a hypertonic pharmaceutical composition comprising the effective amount of a thiosulfate salt. In yet further ~~embodiment~~examples, 200-1,000 µL (e.g., 200-900 µL, 200-800 µL, 200-700 µL, 200-600 µL, 200-500 µL, 200-400 µL, 200-300 µL, 300-900 µL, 300-800 µL, 300-700 µL, 300-600 µL, 300-500 µL, 300-400 µL, 400-900 µL, 400-800 µL, 400-700 µL, 400-600 µL, or 400-500 µL) of the hypertonic pharmaceutical composition are administered to the round window of the subject.

In still further ~~embodiment~~examples, the calculated osmolarity of the hypertonic pharmaceutical composition is 500-5,000 mOsm/L (e.g., 600-5,000 mOsm/L, 700-5,000 mOsm/L, 800-5,000 mOsm/L, 900-5,000 mOsm/L, 1,000-5,000 mOsm/L, 1,500-5,000 mOsm/L, 2,000-5,000 mOsm/L, 2,500-5,000 mOsm/L, 3,000-5,000 mOsm/L, 500-4,000 mOsm/L, 600-4,000 mOsm/L, 700-4,000 mOsm/L, 800-4,000 mOsm/L, 900-4,000 mOsm/L, 1,000-4,000 mOsm/L, 1,500-4,000 mOsm/L, 2,000-4,000 mOsm/L, 2,500-4,000 mOsm/L, 3,000-4,000 mOsm/L, 500-3,000 mOsm/L, 600-3,000 mOsm/L, 700-3,000 mOsm/L, 800-3,000 mOsm/L, 900-3,000 mOsm/L, 1,000-3,000 mOsm/L, 1,500-3,000 mOsm/L, 2,000-3,000 mOsm/L, 2,500-3,000 mOsm/L, 500-2,500 mOsm/L, 600-2,500 mOsm/L, 700-2,500 mOsm/L, 800-2,500 mOsm/L, 900-2,500 mOsm/L, 1,000-2,500 mOsm/L, 1,500-2,500 mOsm/L, 2,000-2,500 mOsm/L, 500-2,000 mOsm/L, 600-2,000 mOsm/L, 700-2,000 mOsm/L, 800-2,000 mOsm/L, 900-2,000 mOsm/L, 1,000-2,000 mOsm/L, 1,500-2,000 mOsm/L, 500-1,500 mOsm/L, 600-1,500 mOsm/L, 700-1,500 mOsm/L, 800-1,500 mOsm/L, 900-1,500 mOsm/L, or 1,000-1,500 mOsm/L).

In some ~~embodiment~~examples, the concentration of the thiosulfate salt in the hypertonic pharmaceutical composition is 0.5M-2.5M (e.g., about 0.05M to about 1.5 M, about 0.05M to about 0.5M, about 0.05M to about 0.2M, about 0.05M to about 0.1M, about 0.1M to about 1.5M, about 0.1M to about 0.5M, about 0.1M to about 0.2M, about 0.2M to about 1.5M, about 0.2M to about 0.5M, about 0.5M to about 1.5M, 0.05M to about 1.0 M, about 0.05M to about 0.5M, about 0.05M to about 0.2M, about 0.05M to about 0.1M, about 0.1M to about 1.0M, about 0.1M to about 0.5M, about 0.1M to about 0.2M, about 0.2M to about 1.0M, about 0.2M to about 0.5M, about 0.5M to about 1.0M, or about 1.0M to about 1.5M).

In certain ~~embodiment~~examples, the effective amount is an amount that produces a plasma thiosulfate concentration that is 30 µM or less at the time the platinum-based antineoplastic agent is administered. In certain ~~embodiments~~examples, the effective amount is 0.1-2.5 mmol of the thiosulfate salt. In particular ~~embodiments~~examples, the effective amount is an amount that produces a maximum thiosulfate concentration of 0.6-10 mmol/L by 1h post administration. In further ~~embodiments~~examples, the effective amount is an amount that produces a thiosulfate concentration of 0.1-2 mmol/L by 7 h post administration in the subject's cochlea.

In some ~~embodiments~~examples, the subject is scheduled to be administered a platinum-based antineoplastic agent within about 1 hour to about 6 hours (e.g., within about 1 hour to about 5 hours,

about 1 hour to about 4 hours, about 1 hour to about 3 hours, about 1 hour to about 2 hours, about 2 hours to about 3 hours, about 2 hours to about 4 hours, about 2 hours to about 5 hours, about 2 hours to about 6 hours, about 3 hours to about 4 hours, about 3 hours to about 5 hours, about 3 hours to about 6 hours, about 4 hours to about 5 hours, about 4 hours to about 6 hours, or about 5 hours to about 6 hours following administration of the thiosulfate salt).

In some ~~embodiments~~examples, the subject is administered a platinum-based antineoplastic agent within about 1 hour to about 6 hours after administration of the thiosulfate salt (e.g., within about 1 hour to about 5 hours, about 1 hour to about 4 hours, about 1 hour to about 3 hours, about 1 hour to about 2 hours, about 2 hours to about 3 hours, about 2 hours to about 4 hours, about 2 hours to about 5 hours, about 2 hours to about 6 hours, about 3 hours to about 4 hours, about 3 hours to about 5 hours, about 3 hours to about 6 hours, about 4 hours to about 5 hours, about 4 hours to about 6 hours, or about 5 hours to about 6 hours after administration of the thiosulfate salt).

In some ~~embodiments~~examples, the subject is administered a platinum-based antineoplastic agent within about 1 hour to about 6 hours before administration of the thiosulfate salt (e.g., within about 1 hour to about 5 hours, about 1 hour to about 4 hours, about 1 hour to about 3 hours, about 1 hour to about 2 hours, about 2 hours to about 3 hours, about 2 hours to about 4 hours, about 2 hours to about 5 hours, about 2 hours to about 6 hours, about 3 hours to about 4 hours, about 3 hours to about 5 hours, about 3 hours to about 6 hours, about 4 hours to about 5 hours, about 4 hours to about 6 hours, or about 5 hours to about 6 hours before administration of the thiosulfate salt).

In one aspect, the present disclosure refers to use of a thiosulfate salt in the manufacture of a medicament for mitigating platinum-induced ototoxicity in a subject in need thereof, wherein the subject was administered a platinum-based neoplastic agent not more than 7 hours prior to when the subject is to be administered the thiosulfate salt, or wherein the subject is scheduled to be administered a platinum-based antineoplastic agent within 4 hours. In another aspect, the present disclosure refers to use of a thiosulfate salt in the manufacture of a medicament for mitigating platinum-induced ototoxicity in a subject in need thereof wherein an effective amount of the thiosulfate salt is to be administered to said subject to produce (i) a plasma thiosulfate C_{max} that is 30 μM or less at the time of administration of a platinum-based antineoplastic agent and (ii) a cochlear thiosulfate C_{max} is at least 30 times greater than a cochlear C_{max} of the platinum-based antineoplastic agent, wherein the cochlear platinum concentrations and the cochlear C_{max} are modeled by a pharmacokinetic simulation of intravenous infusion in a two compartment model.

In yet further ~~embodiments~~examples, the ~~invention~~disclosure is described by the following enumerated items.

1. A method of mitigating platinum-induced ototoxicity in a subject in need thereof, the method comprising administering to the subject an effective amount of a thiosulfate salt, wherein the subject was administered a platinum-based neoplastic agent not more than 7 hours prior to administering the thiosulfate salt or is scheduled to be administered a platinum-based antineoplastic agent within 4 hours.

2. The method of item 1, wherein the effective amount is an amount that produces a plasma thiosulfate concentration that is 30 μM or less at the time the platinum-based antineoplastic agent is administered.

3. A method of mitigating platinum-induced ototoxicity in a subject in need thereof, the method comprising administering to the subject an effective amount of a thiosulfate salt to produce (i) a plasma thiosulfate C_{max} that is 30 μM or less at the time of administration a platinum-based antineoplastic agent and (ii) a cochlear thiosulfate C_{max} is at least 30 times greater than a cochlear C_{max} of the platinum-based antineoplastic agent, wherein the cochlear platinum concentrations and the cochlear C_{max} are modeled by a pharmacokinetic simulation of intravenous infusion in a two compartment model.

4. The method of item 2, wherein the subject was administered a platinum-based neoplastic agent not more than 7 hours prior administering the thiosulfate salt or is scheduled to be administered a platinum-based antineoplastic agent within 4 hours.

CLAIMS

1. ~~A method of mitigating platinum-induced ototoxicity in a subject in need thereof, the method comprising administering to the subject an effective amount~~ Use of a thiosulfate salt in the manufacture of a medicament for mitigating platinum-induced ototoxicity in a subject in need thereof, wherein the subject was administered a platinum-based neoplastic agent not more than 7 hours prior to when the subject is to be ~~administering~~ administered the thiosulfate salt, or wherein the subject is scheduled to be administered a platinum-based antineoplastic agent within 4 hours.

2. The ~~method~~ use of claim 1, wherein the subject was administered a platinum-based neoplastic agent not more than 7 hours prior to when the subject is to be ~~administering~~ administered the thiosulfate salt.

3. The use ~~method~~ of claim 1, wherein the subject is scheduled to be administered a platinum-based antineoplastic agent within 4.5 hours.

4. The use ~~method~~ of claim 1, wherein the subject was administered a platinum-based neoplastic agent not more than 2.5 hours prior to when the subject is to be administered ~~administering~~ the thiosulfate salt.

5. The use ~~method~~ of claim 1, wherein the subject was administered a platinum-based neoplastic agent not more than 1 hour prior to when the subject is to be administered ~~administering~~ the thiosulfate salt.

6. The use ~~method~~ of claim 1, wherein the thiosulfate salt is to be administered auricularly.

7. The use ~~method~~ of claim 6, wherein the thiosulfate salt is to be administered intratympanically, transtympanically, or by inner ear injection.

8. The use ~~method~~ of claim 1, further comprising ~~administering~~ that the platinum-based antineoplastic agent is to be administered.

9. The use ~~method~~ of claim 1, wherein the thiosulfate salt is an alkaline thiosulfate salt, ammonium thiosulfate salt, or a solvate thereof.

10. The use ~~method~~ of claim 1, wherein the ~~effective amount of a~~ thiosulfate salt is to be administered as a hypertonic pharmaceutical composition comprising the ~~effective amount of a~~ thiosulfate salt.

11. The use ~~method~~ of claim 10, wherein 200-1,000 µL of the hypertonic pharmaceutical composition are to be administered to the round window of the subject.

12. The ~~method~~ use of claim 10, wherein the calculated osmolarity of the hypertonic pharmaceutical composition is 500-5,000 mOsm/L.

13. The use ~~method~~ of claim 10, wherein the concentration of the thiosulfate salt in the hypertonic pharmaceutical composition is 0.5M-2.5M.

14. The use ~~method~~ of claim 1, wherein the thiosulfate salt is to be administered in ~~effective amount is~~ an amount that produces a plasma thiosulfate concentration that is 30 µM or less at the time the platinum-based antineoplastic agent is to be administered.

15. The use ~~method~~ of claim 1, wherein the ~~effective~~ amount is 0.1-2.5 mmol of the thiosulfate salt.

16. The use ~~method~~ of claim 1, wherein the thiosulfate salt is to be administered in ~~effective amount is~~ an amount that produces a maximum thiosulfate concentration of 0.6-10 mmol/L by 1h post administration.

17. The use ~~method~~ of claim 1, wherein the thiosulfate salt is to be administered ~~effective amount is~~in an amount that produces a thiosulfate concentration of 0.1-2 mmol/L by 7 h post administration in the subject's cochlea.

18. ~~A method of mitigating platinum-induced ototoxicity in a subject in need thereof, the method comprising administering to the subject~~Use of ~~an effective amount of~~ a thiosulfate salt in the manufacture of a medicament for mitigating platinum-induced ototoxicity in a subject in need thereof wherein an effective amount of the thiosulfate salt is to be administered to said subject to produce (i) a plasma thiosulfate C_{max} that is 30 µM or less at the time of administration of a platinum-based antineoplastic agent and (ii) a cochlear thiosulfate C_{max} is at least 30 times greater than a cochlear C_{max} of the platinum-based antineoplastic agent, wherein the cochlear platinum concentrations and the cochlear C_{max} are modeled by a pharmacokinetic simulation of intravenous infusion in a two compartment model.

19. The use ~~method~~ of claim 18, wherein the effective amount of a thiosulfate salt is to be administered within 3 hours before ~~administering~~ a platinum-based antineoplastic agent is to be administered or within 4 hours after ~~administering~~ the platinum-based antineoplastic agent is to be administered.

20. The use ~~method~~ of claim 18, wherein the effective amount of a thiosulfate salt is to be administered within 4.5 hours before ~~administering~~ a platinum-based antineoplastic agent is to be administered or within 2.5 hours after ~~administering~~ the platinum-based antineoplastic agent is to be administered.