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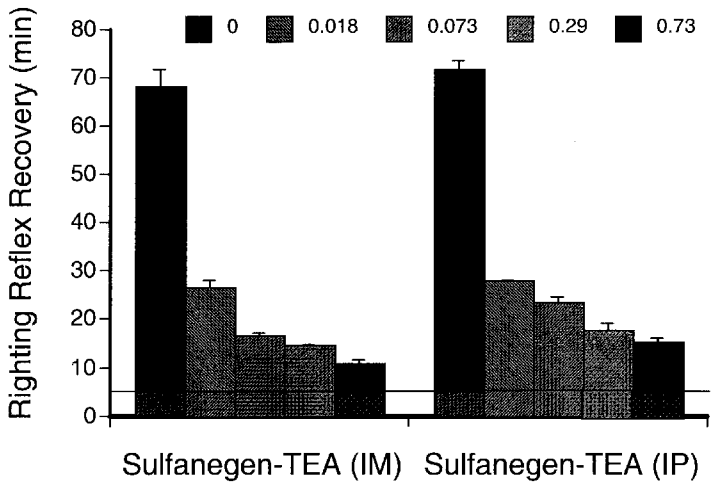
(54) **Title**: CYANIDE ANTIDOTES

Figure 1



(57) **Abstract**: The invention provides salts of sulfanegen and methods for their use.

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CYANIDE ANTIDOTES

Cross-reference to Related Applications

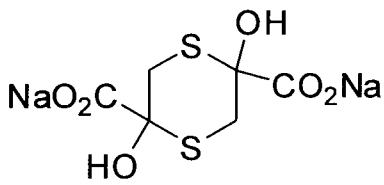
This patent application claims the benefit of priority of U.S. application serial No. 61/327,378, filed April 23, 2010, which application is herein incorporated by reference.

Statement of Government Support

This invention was made with government support under grant numbers 5U01-NS058087 and 3U54-NS063718 awarded by the National Institutes of Health. The government has certain rights in the invention.

Background

Currently available cyanide antidotes must be administered via intravenous (IV) administration. Sulfanegen sodium can be an effective cyanide antidote when administered via an intraperitoneal (IP) injection.



Sulfanegen sodium

(Also, *see, e.g*, WO 2008/005806 and Cooper *et al.*, *Journal of Biological Chemistry*, *257*, 816-826 (1982).) However, this salt of sulfanegen is not sufficiently water soluble for effective intramuscular (IM) administration. Thus, in a mass casualty setting such as a terrorist attack or a major chemical accident, large numbers of cyanide-exposed victims are likely to be untreated in any rescue attempts using currently-available cyanide antidotes. Therefore, there is a need for cyanide antidotes amenable to more rapid delivery methods, such as via an autoinjector. Ideally, larger doses of antidote should be administered rapidly for maximal efficacy, inflammation at the site of administration should be minimal, and the antidote should be highly water soluble.

Summary of Certain Embodiments of the Invention

The present invention , as described herein, provides salts of sulfanegen including triethanolamine (TEA), diethanolamine (DEA), monomethylaminoethanol (MMAE) and dimethylaminoethanol (DMAE) salts that are significantly more water soluble than the sodium salt of sulfanegen. Accordingly, these new forms of sulfanegen are useful as cyanide antidotes. These new forms are effective when administered by injection (*e.g.*, IM or IV or IP) as well as when administered orally, and are inexpensive and rapidly acting, *e.g.*, when administered by IM injection.

Brief Description of the Figures

Figure 1 depicts the effects of sulfanegen TEA 5 min post cyanide exposure.

Figure 2 depicts the effects of sulfanegen TEA 10 min post cyanide exposure.

Figure 3 depicts the effects of sulfanegen TEA 20 min post cyanide exposure.

Figure 4 depicts the effects of sulfanegen TEA 30 min post cyanide exposure.

Figure 5 depicts the effects of sulfanegen TEA 40 min post cyanide exposure.

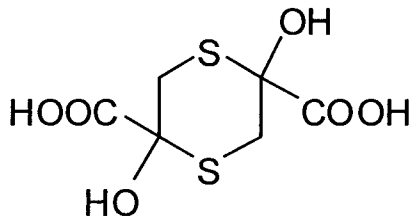
Figure 6 depicts the effects of sulfanegen TEA vs FDA approved antidotes in the mouse model. CN = first column, H = second column, N/T = third column, sulfanegen sodium = fourth column. CN = cyanide treatment controls (no drug); H = hydroxocobalamin; N/T = combination of sodium nitrite and sodium thiosulfate.

Figure 7 depicts the changes in OxyHb and DeoxyHb in response to cyanide and antidote treatment (IM) in rabbit model.

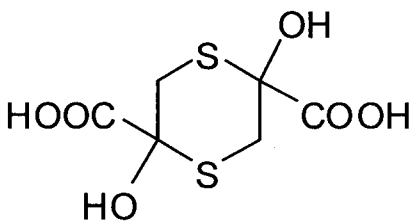
Figures 8a and 8b depict the cyanide levels and lactate levels in the swine cyanide models for IM treatment with sulfanegen TEA.

Detailed Description

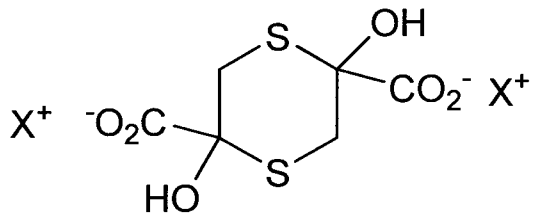
Accordingly, certain embodiments provide a triethanolamine, diethanolamine, monomethylaminoethanol or dimethylaminoethanol salt of a compound of the formula



In certain embodiments the invention provides a triethanolamine (TEA) or diethanolamine (DEA) salt of a compound of the formula

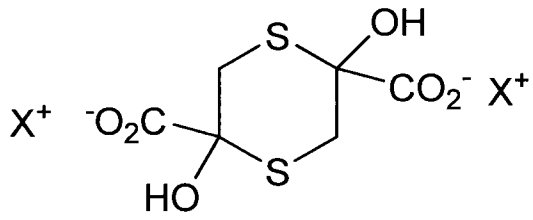


Certain embodiments provide a salt of the following formula



wherein X^+ is TEA or DEA in protonated form.

Certain embodiments provide a salt of the following formula



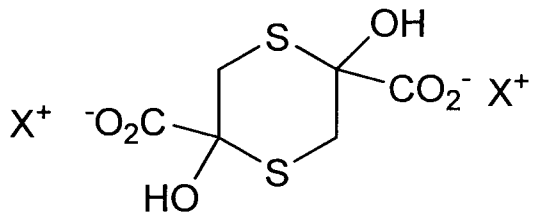
wherein X^+ is triethanolamine, diethanolamine, monomethylaminoethanol or dimethylaminoethanol in protonated form.

In certain embodiments, the salt is a TEA salt.

In certain embodiments, the salt is a DEA salt.

In certain embodiments, the salt is a monomethylaminoethanol or dimethylaminoethanol salt.

Certain embodiments of the invention provide a salt of the following formula



wherein X^+ is melamine, glucosamine, ethanolamine, tromethamine, N-methylaminoethanol and N,N-dimethylaminoethanol.

Certain embodiments provide a pharmaceutical composition comprising a salt as described herein and a pharmaceutically acceptable carrier.

In certain embodiments, the composition is adapted for intramuscular (IM) administration.

In certain embodiments, the composition is adapted for intravenous (IV) administration.

In certain embodiments, the composition is adapted for oral administration.

In certain embodiments, the composition is in unit dosage form.

In certain embodiments, the composition comprises about 1-10 grams (*e.g.*, about 3-8 grams) of the salt.

In certain embodiments, the composition comprises about 1-12 grams of the salt.

Certain embodiments provide a method of treating cyanide poisoning in a subject in need of such treatment, comprising administering to a subject a therapeutically effective amount of the salt as described herein, or the composition as described herein.

In certain embodiments, the salt or composition is administered intramuscularly (IM).

In certain embodiments, the salt or composition is administered intravenously (IV).

In certain embodiments, the salt or composition is administered orally.

Certain embodiments provide a salt as described herein for use in therapy.

Certain embodiments provide a salt as described herein for use in treating cyanide poisoning.

Certain embodiments provide a salt as described herein for use in medical treatment or diagnosis.

Certain embodiments provide the use of a salt as described herein to prepare a medicament useful for treating cyanide poisoning in an animal.

Thus, the present salts may be administered, *e.g.*, IM, IV, or orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should generally contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained. The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules

may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously (IV), intraperitoneally (IP), or intramuscularly (IM) by infusion or injection, *e.g.*, using an autoinjector. The compounds may be administered using an autoinjector. Solutions of the active compound can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. The ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum

drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

Useful dosages of the compounds can be determined, *e.g.*, by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

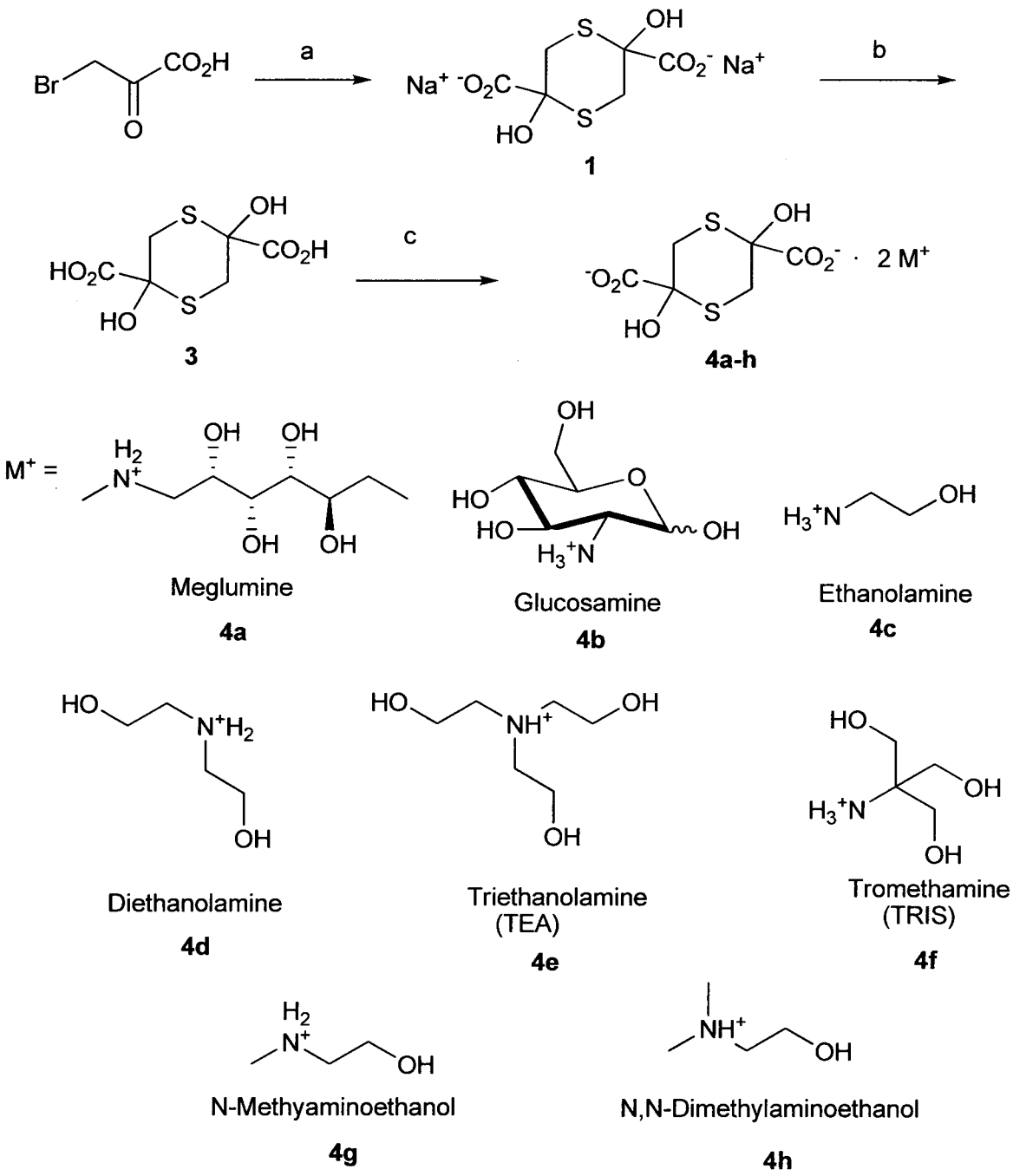
The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day.

Compounds of the invention can also be administered in combination with other therapeutic agents, for example, other agents that are useful for the treatment of cyanide exposure. Accordingly, in one embodiment the invention also provides a composition comprising sulfanegen TEA and/or sulfanegen DEA, at least one other therapeutic agent, and a pharmaceutically acceptable diluent or carrier.

The invention also provides a kit comprising sulfanegen TEA and/or sulfanegen DEA, packaging material, and instructions for administration. The kit may also contain at least one other therapeutic agent.

Scheme 1 illustrates a synthesis that that was used to prepare salts of sulfanegen including compounds of the invention. Scheme 1illustrates the synthesis of salts in the ratio of about 2 : 1 (M^+ : compound 3). The invention also includes other salt ratios, including but not limited to ratios of about 1 : 1. The invention also includes other physical forms (e.g. complexes) of M^+ and compound 3 including but not limited to cocrystals.

Scheme 1

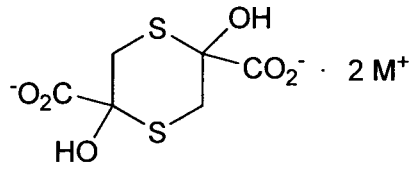


Reagents and conditions for the synthesis of Scheme 1: (a) 2 molar equivalent NaHS, ethanol; (b) Dowex-50WX8, H^+ form; (c) 2 equivalent of a biocompatible amine (M).

Accordingly, the present invention also includes salts of sulfanegen wherein the salt is melamine (4a), glucosamine (4b), ethanolamine (4c), tromethamine (4f), N-methylaminoethanol (4g) and N,N-dimethylaminoethanol (4h).

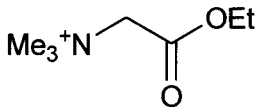
Scheme 2 depicts the betaine ethyl ester and choline salts of sulfanegen.

Scheme 2



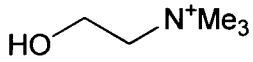
4j and **4k**

M^+ =



Betaine ethyl ester

4j



Choline

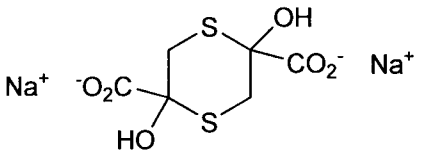
4k

The invention will now be illustrated by the following non-limiting Examples.

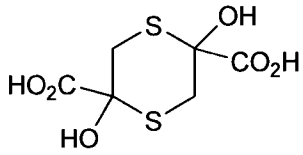
Example 1. Water solubility of sulfanegen salts

The exchange of sodium in sulfanegen sodium with pharmaceutically acceptable amines provided the salts as depicted below and in Scheme 1 and Scheme 2. Surprisingly, both TEA and DEA sufficiently improved the aqueous solubility and physical characteristics (see Table 1). There was no structure activity relationship between the salt formulations and solubility.

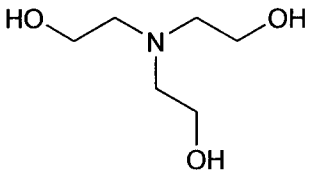
Other unexpected results include the solubility of the monomethylaminoethanol (MMAE) salt and the dimethylaminoethanol (DMAE). The choline salt of sulfanegen had a solubility of 1.2 M in water while the ethanolamonium salt, had a solubility of 1.39 M in water. Surprisingly, the solubility of the monomethylaminoethanol (MMAE) salt was three-fold higher than the choline salt and the dimethylaminoethanol (DMAE) salt gave an approximate four-fold increase in aqueous solubility. These amines are all aminoethanol derivatives differing only in methylation of the amino moiety. The solubility of their sulfanegen salts however did not follow a predictable pattern.



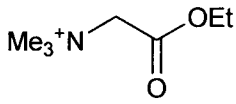
1



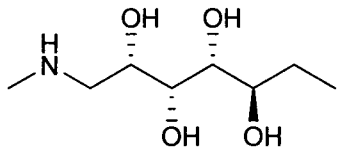
3



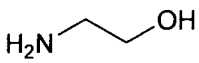
Triethanolamine (TEA)



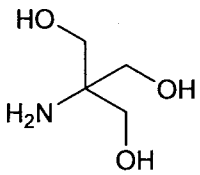
Betaine ethyl ester



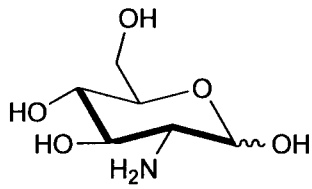
Meglumine



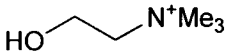
Ethanolamine



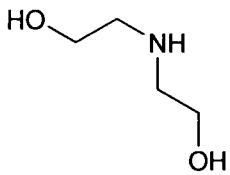
Tromethamine (TRIS)



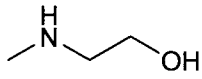
Glucosamine



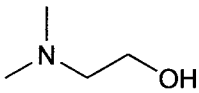
Choline



Diethanolamine



N-Methyaminoethanol



N,N-Dimethylaminoethanol

Table 1. Salt formulations of Sulfanegen

Formulation salts (compound number)	Appearance	Solubility (mol/L)	Melting point (°C)
Sodium **(1)**	White solid	0.4	132-134
Free acid **(3)**	White solid	< 0.1	148-150
Triethanolamine (TEA) **(4e)**	White solid	2.07-2.13	122-123
Tromethamine (TRIS) **(4f)**	White solid	0.38	125-127
Meglumine **(4a)**	Hygroscopic glass	3.0	119-120 (dec)
Glucosamine **(4b)**	White solid	0.13	126-128 (dec)
Choline **(4k)**	White solid	1.2	114-116
Ethanolamine (EA) **(4c)**	White solid	1.39	73-75
Diethanolamine (DEA) **(4d)**	White solid	3.5	104-105
Betaine ethyl ester **(4j)**	White solid	< 0.1	108-110
N-Methylaminoethanol (MMAE) **(4g)**	White solid	4.7	101-103
N,N-Dimethylaminoethanol (DMAE) **(4h)**	White solid	5.4	121-122

Example 2. Mouse Model

The efficacy of cyanide antidotes was measured as follows. A dose less than the LD50 was administered. This causes 'knock-down' or loss of neuromuscular coordination. The efficacy of antidote was measured by reduction in time for the animal to recover neuromuscular coordination. Swiss albino male mice were treated with cyanide (ip) at a dose that requires 60-70 min for recovery. Briefly, the 'knocked-down' animal was placed on a wire mesh and inverted. The time for the animal to right itself to the top of the wire mesh screen was measured as the recovery time and the antidotal efficacy is measured as the reduction of this recovery time vs. the cyanide alone animals. Statistically this is much more powerful than LD50. As depicted in Figures 1, 2, 3, 4 or 5 sulfanegen TEA, administered IM or IP, is an effective cyanide antidote. Figure 6 depicts the effects of sulfanegen TEA vs FDA approved antidotes in the mouse model.

Example 3: Rabbit efficacy.

Figure 7 depicts the changes in OxyHb and DeoxyHb in response to cyanide and antidote treatment (IM) in rabbit model. Rapid recovery was demonstrated in the treated animals.

Example 4: Toxicity study of sulfanegen salts

Sulfanegen-TEA was dissolved in sterile saline and the dose administered in two injections, one in each leg muscle. There were four mice per group and three groups. A high dose of 8.9 mmol/kg (4789 mg/kg), was given first, followed by a low dose of 2.5 mmol/kg (1320 mg/kg). This low dose is approximately 3.3 times that of the highest dose given in characterization of Sulfanegen-TEA which is 0.73 mmol/kg (393 mg/kg). Increasing doses were given from the lowest dose until LD50. The first increased dose of 3.6 mmol/kg (1939 mg/kg) achieved that goal. Death when it occurred was within 5 min of the injections. The mice were watched closely for two hrs following the injections and then checked daily for one week.

All injections were bilateral in the thigh leg muscle, IM. The volumes did not exceed 60µl per leg muscle injection. Phosphate buffered saline kept the sulfanegen salt solutions within a 7.5-8.5 pH range. None of the animals showed signs of discomfort at the time of the injections. The Sulfanegen Na salt went into solution by heating with hot tap water and repeated vortexing. The volumes injected for the Sulfanegen sodium salt were greater than the other more soluble Sulfanegen salts. Each group was an n of four mice. At post injection 24 hours, all surviving animals passed the Righting Reflex Recovery within one minute and exhibited normal behaviors.

Sulfanegen salt	2.45 mmoles/kg dose	4.9 mmoles/kg dose
Sulfanegen Na (compound 2)	Passed Righting Reflex Recovery within 5-7 min. Mice alert and moving about the cage.	LD 100 within 5-8 min.
Sulfanegen TEA (compound 4e)	Passed Righting Reflex Recovery within 4-7 min. Mice alert and moving about the cage.	LD 100 within 8-9 min.
Sulfanegen MMAE (compound 4g)	Passed Righting Reflex Recovery within 66-75 min. Hindquarters dysfunction began within 5 min of injections.	LD 100 within 7 min.
Sulfanegen DMAE (compound 4h)	LD 75 within 8 min. The one remaining animal had hindquarters dysfunction and passed the Righting Reflex Recovery at 41 min post injections.	LD 100 within 4-8 min.
Sulfanegen DEA (compound 4d)	Passed Righting Reflex Recovery within 6-11 min. Mice alert and moving about the cage.	LD 25 within 11 min. Passed Righting Reflex Recovery within 44-109 min.
Phosphate buffered saline, pH 7.5 1min RRR after 50µl injection each thigh		

Example 5: Swine cyanide models for IM treatment with sulfanegen.

Figure 8a and 8b depict the swine cyanide models for IM treatment with sulfanegen TEA. Figure 8a depicts cyanide levels in placebo (control) and sulfanegen TEA treated animals while Figure 8b depicts lactate levels in placebo (control) and sulfanegen TEA treated animals.

Piglets treated with CN and no antidote (n= 4) died while piglets treated with CN and sulfanegen TEA (320 mg/kg, iv) all survived (n = 4) with normal blood chemistry. Two of the piglets treated with CN and sulfanegen TEA had a brief increase in lactate during recovery but lactate levels returned to baseline levels during the recovery. Piglets treated with CN (iv) and sulfanegen TEA (im) all survived (n = 5).

Piglets (n = 2) treated with sulfanegen TEA (200 mg/kg) and no cyanide demonstrated normal blood chemistry and normal behavior. Anesthetized piglets (n = 2) treated with triethanolamine hydrochloride (138 mg/kg, iv) demonstrated normal blood chemistry after recovery, however, a temporary increase in lactate was observed.

Example 6: Preparation of compounds 4a - 4h

General procedure for the preparation of compounds **4a-4h**.

A solution of disodium 2,5-dihydroxy-1,4-dithiane-2,5-dicarboxylic acid tetrahydrate (prepared by the method of WO2008/005806) (0.25 g, 0.70 mmol) in H_2O (7 mL) was applied to a column of ion-exchange resin Dowex 50WX8-200 (H^+; 3 mL, 5 meq), and was eluted with H_2O until the eluate tested negative for the presence of dithiane by $KMnO_4$ stain on TLC silica plate to provide compound 3 in solution. The eluate was treated with a solution of the desired amine (1.40 mmol) in H_2O (15 mL), and the resulting solution was allowed to stir at room temperature for 10 min. The solution was subsequently lyophilized to yield a white solid.

Characterization data for 2,5-dihydroxy-1,4-dithiane-2,5-dicarboxylic acid (**3**). Yield 99%. ^{1}H NMR (300 MHz, D_2O): δ 3.01 (2H, d, J = 14.4 Hz, major isomer), 3.21 (2H, d, J = 14.4 Hz, minor isomer), 3.45 (2H, d, J = 14.4 Hz, minor isomer), 3.90 (2H, d, J = 14.4 Hz). ^{13}C NMR (75 MHz, D_2O): δ 35.2, 37.3, 76.0, 78.8, 174.5, 174.7. Anal. Calcd for $C_6H_8O_6S_2$: C, 30.00; H, 3.36; S, 26.69. Found: C, 30.12; H, 3.44; S, 26.48.

Compound **4a**:

2.5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-((*2R,3R,4R,5S*)-6-methylaminohexane-1,2,3,4,5-pentol) trihydrate salt (**4a**). Compound **4a** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.79 (6H, s), 2.83 (2H, d, J = 14.4 Hz, major isomer), 3.09 (2H, d, J = 14.4 Hz, minor isomer), 3.18-3.27 (5H, m), 3.58 (2H, d, J = 14.4 Hz, minor isomer), 3.65-369 (5H, m), 3.76-3.79 (2H, m), 3.82-3.84 (2H, m), 3.87 (2H, d, J = 14.4 Hz, major isomer), 4.10-4.13 (2H, m). ^{13}C NMR (150 MHz, D_2O): δ 32.96, 35.92, 51.07, 62.64, 68.03, 70.51, 70.66, 70.87, 77.03, 176.84. Anal. Calcd for $C_{20}H_{42}N_2O_{16}S_2 \cdot 3H_2O$: C, 35.08; H, 7.07; N, 4.09; S, 9.37. Found: C, 34.94; H, 6.87; N, 4.00; S, 9.67. mp: 119-120 ^oC (dec.).

Compound **4b:**

2,5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-((3*R*,4*R*,5*S*)-3-Amino-6-(hydroxymethyl)-oxane-2,4,5-triol) salt (**4b**). Compound **4b** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H (600 MHz, D_2O): δ 2.86 (d, 2H, major isomer), 3.02 (m, 1H), 3.10 (d, 2H, minor isomer), 3.32 (dd, 1H), 3.48-3.55 (m, 3H), 3.58 (d, 2H, minor isomer), 3.68-3.71 (m, 1H), 3.75-3.82 (m, 2H), 3.87 (d, 2H, major isomer), 3.90-3.94 (m, 4H), 4.96 (d, 1H), 5.46 (s, 1H). Anal. Calcd for $C_{18}H_{34}N_2O_{16}S_2 \cdot 1.5\ H_2O$: C, 34.56; H, 5.96; N, 4.48; S, 10.25. Found C, 34.65; H, 6.01; N, 4.47; S, 10.20. mp: 126-128 °C.

Compound **4c**:

2.5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-(2-aminoethanol) salt (**4c**). Compound **4c** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.86 (2H, d, J = 14.4 Hz, major isomer), 3.10 (2H, d, J = 14.4 Hz, minor isomer), 3.15 (4H, t, J = 4.8 Hz), 3.57 (2H, d, J = 14.4 Hz, minor isomer), 3.83 (4H, t, J = 4.8 Hz), 3.86 (2H, d, J = 14.4 Hz, minor isomer). ^{13}C NMR (150 MHz, D_2O): δ 35.94, 41.26, 57.59, 77.04, 176.78. Anal. Calcd for $C_{10}H_{22}N_2O_7S_2 \cdot 0.8H_2O$: C, 31.87; H, 6.31; N, 7.43; S, 17.02. Found: C, 31.91; H, 6.39; N, 7.32; S, 17.11. mp: 73-75 °C.

Compound **4d**:

2.5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-(2,2'-iminodiethanol) salt (**4d**). Compound **4d** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.85 (2H, d, J = 14.4 Hz, major isomer), 3.10 (2H, d, J = 14.4 Hz, minor isomer), 3.26 (8H, t, J = 4.8 Hz), 3.57 (2H, d, J = 14.4 Hz, minor isomer), 3.86 (2H, d, J = 14.4 Hz, minor isomer), 3.89 (8H, t, J = 4.8 Hz). ^{13}C NMR (150 MHz, D_2O): δ 35.95, 48.87, 56.46, 77.03, 176.79. Anal. Calcd for $C_{10}H_{30}N_2O_{10}S_2$: C, 37.32; H, 6.71; N, 6.22; S, 14.23. Found: C, 37.50; H, 6.68; N, 6.20; S, 14.16. Elucidation of structure via X-Ray crystallography. Crystals were grown from MeOH/Et_2O. mp: 104-105 °C.

Compound **4e**:

2,5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-(2,2',2"-nitrilotriethanol) salt (**4e**). Compound **4e** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.87 (2H, d, J = 14.4 Hz, major isomer), 3.11 (2H, d, J = 14.4 Hz, minor isomer),

3.52 (12H, t, J = 5.4 Hz), 3.60 (2H, d, J = 14.4 Hz, minor isomer), 3.89 (2H, d, J = 14.4 Hz), 3.99 (12H, t, J = 5.4 Hz). ^{13}C NMR (150 MHz, D_2O): δ 36.6, 55.6, 55.9, 77.6, 177.4. Anal. Calcd for $C_{18}H_{38}N_2O_{12}S_2$: C, 40.14; H, 7.11; N, 5.20; S, 11.91. Found: C, 39.84; H, 7.18; N, 5.32; S, 11.63. Mp: 122-123 °C.

Compound **4f**:

2,5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-(2-amino-2-hydroxymethyl-propane-1,3-diol) salt (**4f**). Compound **4f** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (D_2O): δ 2.84 (d, J = 14.1 Hz, 2H), 3.73 (s 12H) 3.85 (d, J = 14.1 Hz, 2H), ^{13}C NMR (D_2O): δ 36.5, 59.9, 62.0, 77.6, 177.6, Anal. Calcd for C 31.34%, H 6.76%, N 5.22%, Found C 31.63%, H 6.56%, N 5.26%, mp 125.5-127 °C (dec).

Compound **4g**:

2.5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-[(2-methylamino)ethanol] salt (**4g**). Compound **4g** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.77 (6H, s), 2.86 (2H, d, J = 14.4 Hz, major isomer), 3.10 (2H, d, J = 14.4 Hz, minor isomer), 3.20 (4H, t, J = 5.4 Hz), 3.58 (2H, d, J = 14.4 Hz, minor isomer), 3.86 (4H, t, J = 5.4 Hz), 3.88 (2H, d, J = 14.4 Hz, major isomer). ^{13}C NMR (150 MHz, D_2O): δ 32.58,35.94, 50.46, 56.39, 77.04, 114.15, 176.81. Anal. Calcd for $C_{12}H_{26}N_2O_8S_2$: C, 36.91; H, 6.71; N, 7.17; S, 16.42. Found: C, 36.75; H, 6.77; N, 7.16; S, 16.31. mp: 101-103 °C.

Compound **4h**:

2.5-Dihydroxy-1,4-dithiane-2,5-dicarboxylic acid, bis-[(2-dimethylamino)ethanol] salt (**4h**). Compound **4h** was prepared by the general procedure of Example 6 in 99% yield. ^{1}H NMR (600 MHz, D_2O): δ 2.85 (2H, d, J = 14.4 Hz, major isomer), 2.94 (12H, s), 3.09 (2H, d, J = 14.4 Hz, minor isomer), 3.31 (4H, t, J = 5.4 Hz), 3.57 (2H, d, J = 14.4 Hz, minor isomer), 3.86 (2H, d, J = 14.4 Hz, major isomer), 3.91 (4H, t, J = 5.4 Hz). ^{13}C NMR (150 MHz, D_2O): δ 35.98, 42.74, 55.17, 58.75, 77.05, 176.76. Anal. Calcd for $C_{14}H_{30}N_2O_8S_2$: C, 40.18; H, 7.22; N, 6.69; S, 15.32. Found: C, 40.07; H, 7.25; N, 6.67; S, 15.29. mp: 121-122 °C.

All publications, patents and patent applications cited herein are incorporated herein by reference. While in the foregoing specification this invention has been described in relation to

certain embodiments thereof, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details described herein may be varied considerably without departing from the basic principles of the invention.

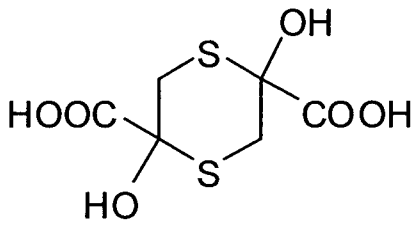
The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (*i.e.*, meaning "including, but not limited to") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

Claims

What is claimed is:

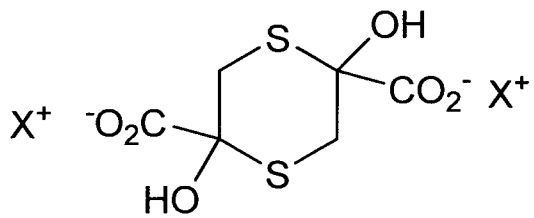
1. A triethanolamine, diethanolamine, monomethylaminoethanol or dimethylaminoethanol salt of a compound of the formula



2. The salt of claim 1 wherein the salt is a triethanolamine or diethanolamine salt.

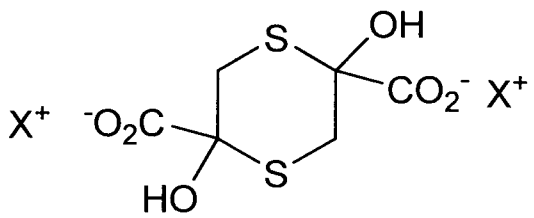
3. The salt of claim 1 wherein the salt is a monomethylaminoethanol or dimethylaminoethanol salt.

4. The salt of claim 1, which is a salt of the following formula



wherein X^+ is triethanolamine, diethanolamine, monomethylaminoethanol or dimethylaminoethanol in protonated form.

5. The salt of claim 1, which is a salt of the following formula



wherein X^+ is triethanolamine or diethanolamine in protonated form.

6. The salt of claim 1 or claim 5, which is a triethanolamine salt.

7. The salt of claim 1 or claim 5, which is a diethanolamine salt.

8. A pharmaceutical composition comprising a salt as described in any one of claims 1-7 and a pharmaceutically acceptable carrier.

9. The composition of claim 8 that is adapted for intramuscular (IM) administration.

10. The composition of claim 8 that is adapted for intravenous (IV) administration.

11. The composition of claim 8 that is adapted for oral administration.

12. The composition of any one of claims 8-11 that is in unit dosage form.

13. The composition of claim 12 that comprises about 1-12 grams of the salt.

14. The composition of claim 12 that comprises about 3-8 grams of the salt.

15. A method of treating cyanide poisoning in a subject in need of such treatment, comprising administering to a subject a therapeutically effective amount of the salt of any one of claims 1-7, or the composition of any one of claims 8-14.

16. The method of claim 15, wherein the salt or composition is administered intramuscularly (IM).

17. The method of claim 15, wherein the salt or composition is administered intravenously (IV) .

18. The method of claim 15, wherein the salt or composition is administered orally.

19. A salt according to any one of claims 1-7 for use in therapy.

20. A salt according to any one of claims 1-7 for use in treating cyanide poisoning.

21. A salt as described in any one of claims 1-7 for use in medical treatment or diagnosis.

22. The use of a salt as described in any one of claims 1-7 to prepare a medicament useful for treating cyanide poisoning in an animal.

Figure 1

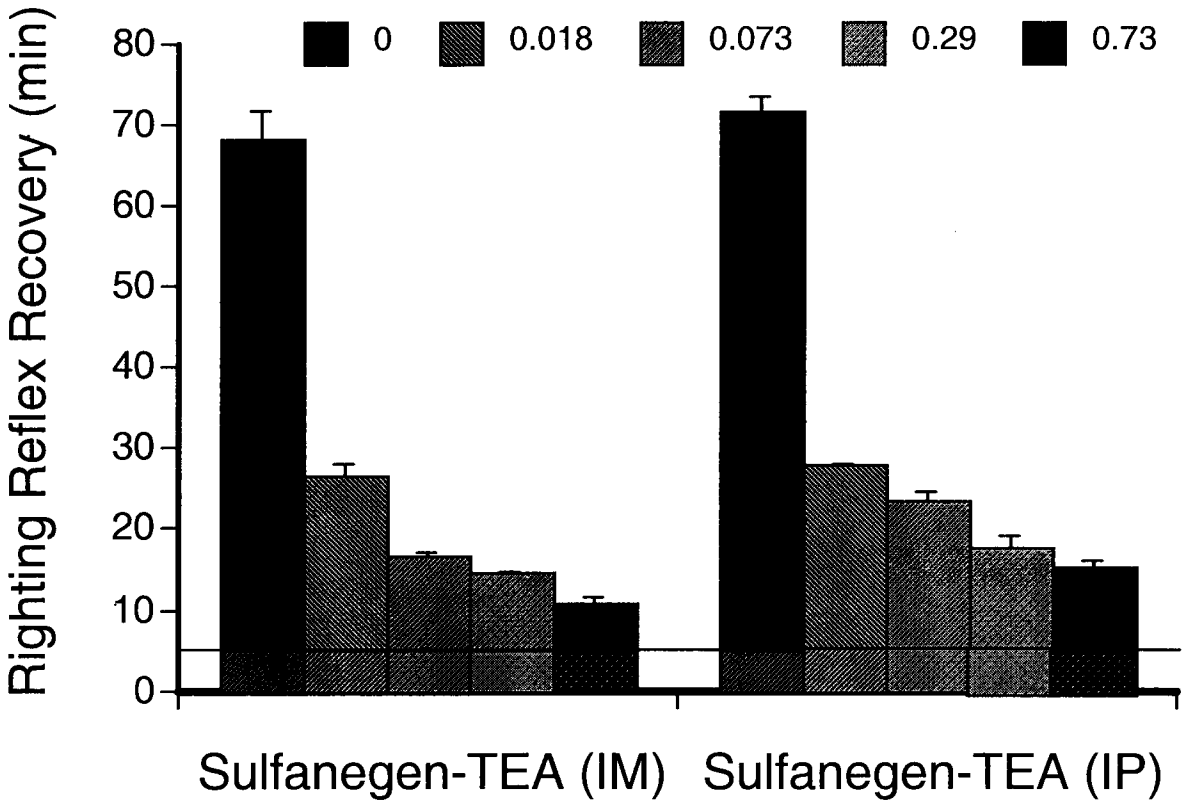


Figure 2

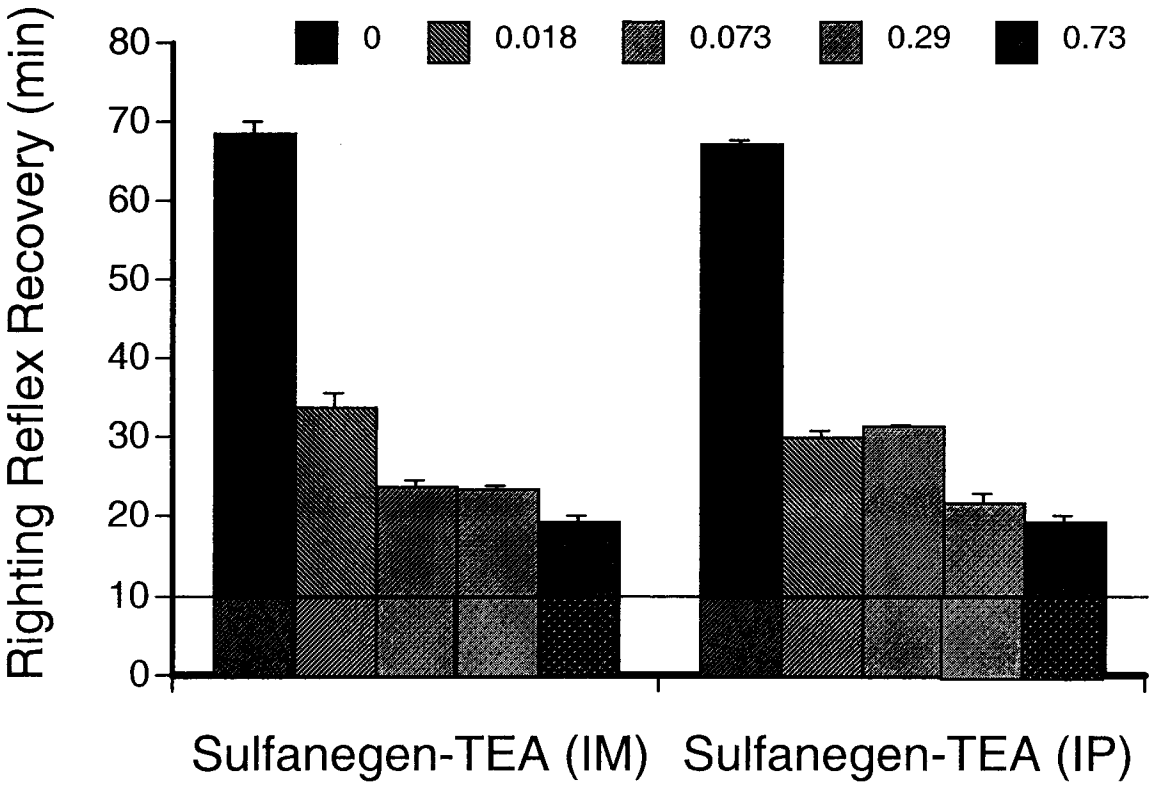


Figure 3

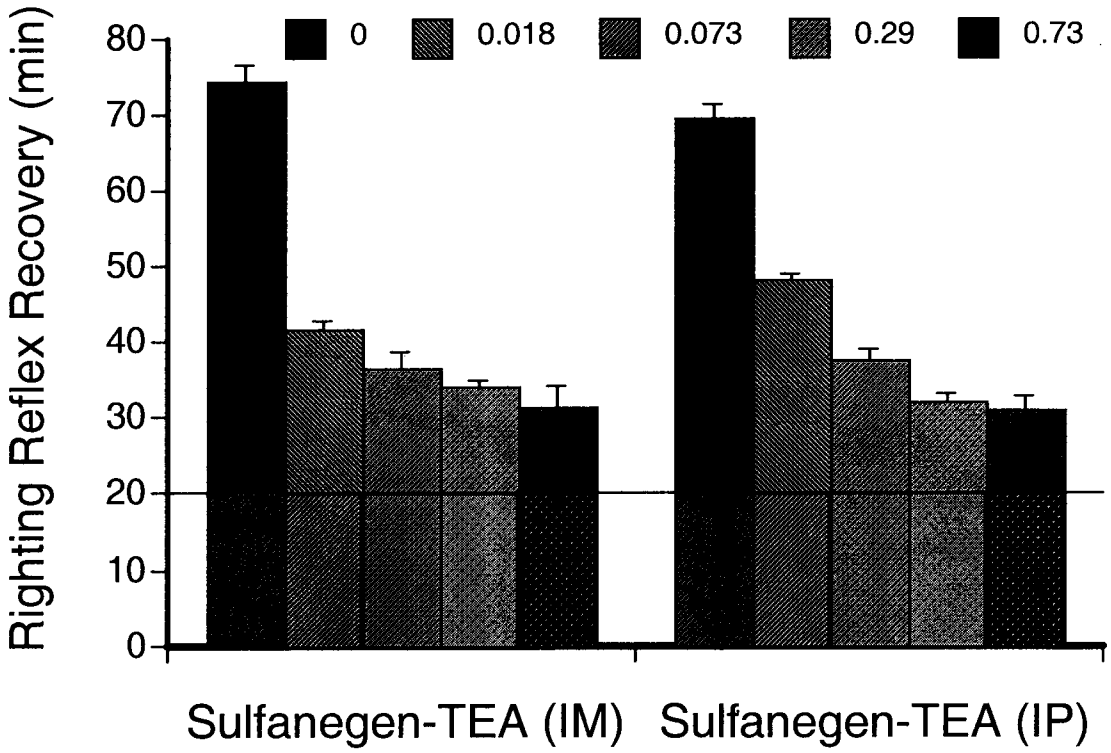


Figure 4

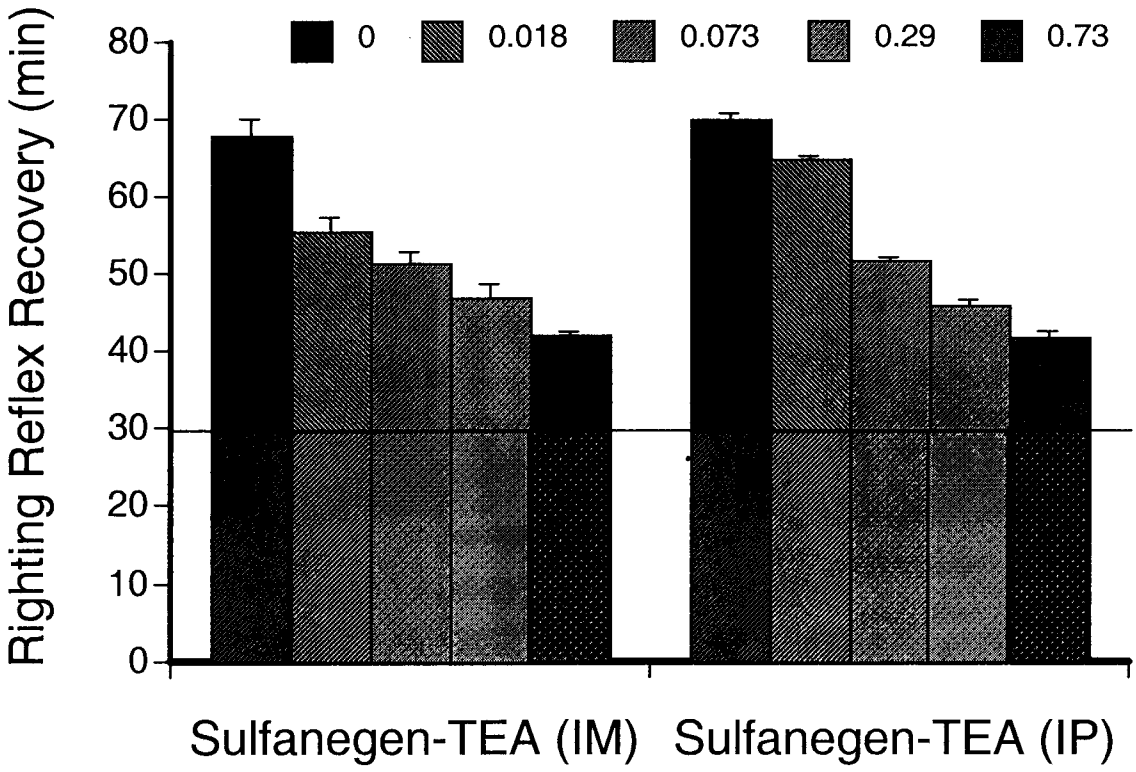


Figure 5

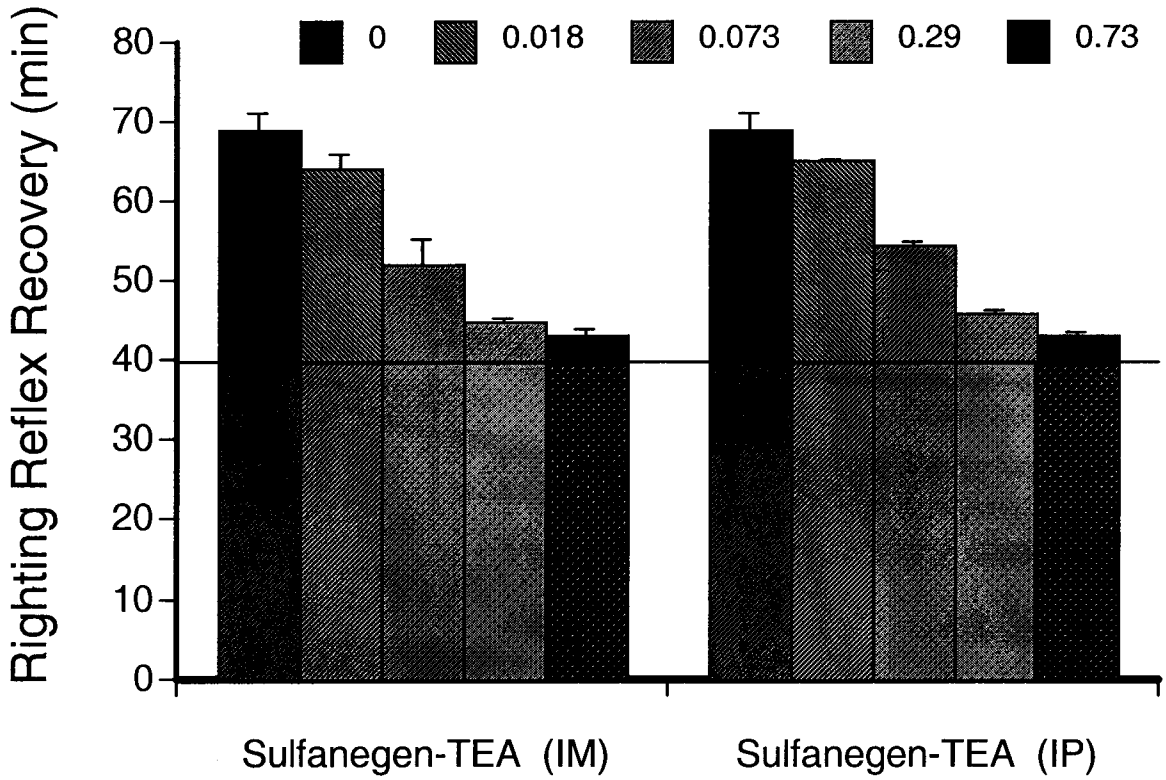


Figure 6

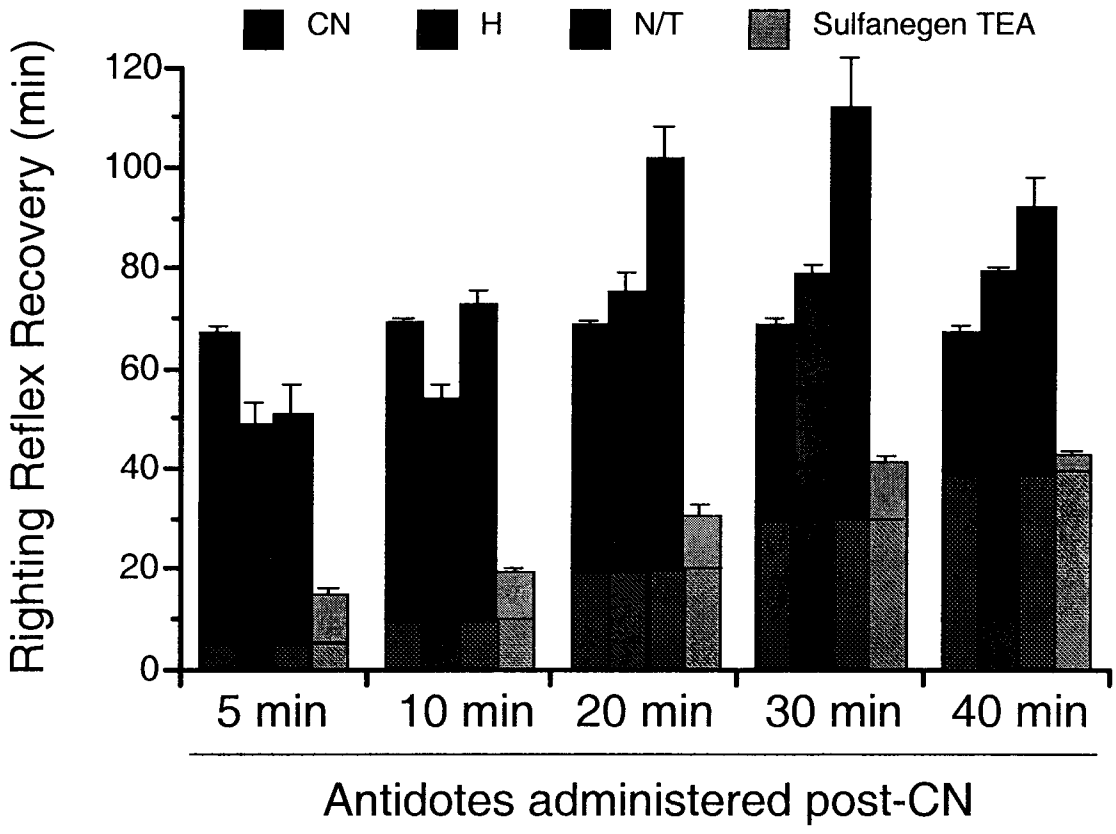


Figure 7

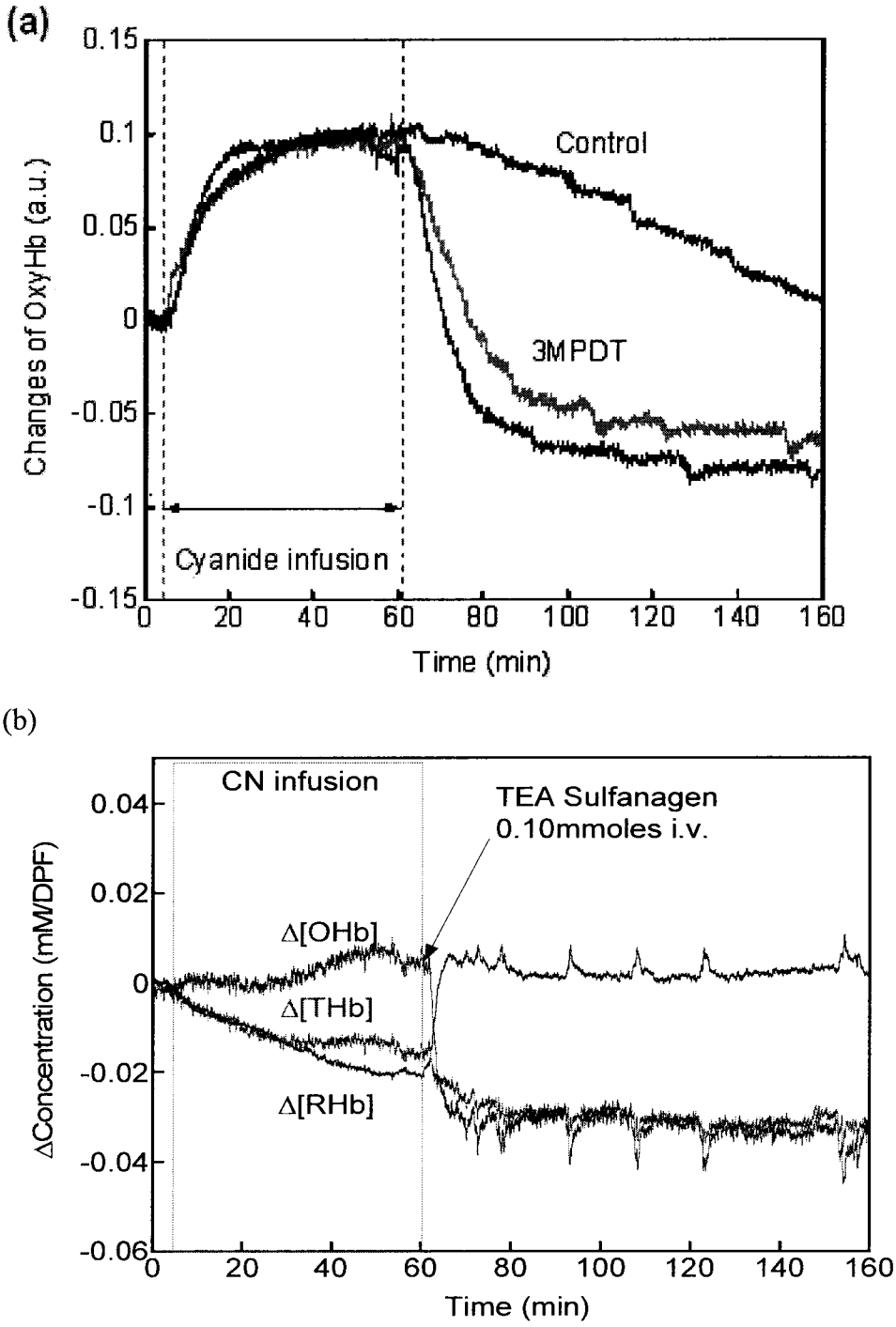

(a)
Changes of OxyHb (a.u.)
0.15
0.1
0.05
0
-0.05
-0.1
-0.15
Control
3MPDT
Cyanide infusion
0
20
40
60
80
100
120
140
160
Time (min)
(b)
ΔConcentration (mM/DPF)
0.04
0.02
0
-0.02
-0.04
-0.06
CN infusion
TEA Sulfanagen
0.10mmoles i.v.
Δ[OHb]
Δ[THb]
Δ[RHb]
0
20
40
60
80
100
120
140
160
Time (min)

Figure 8a

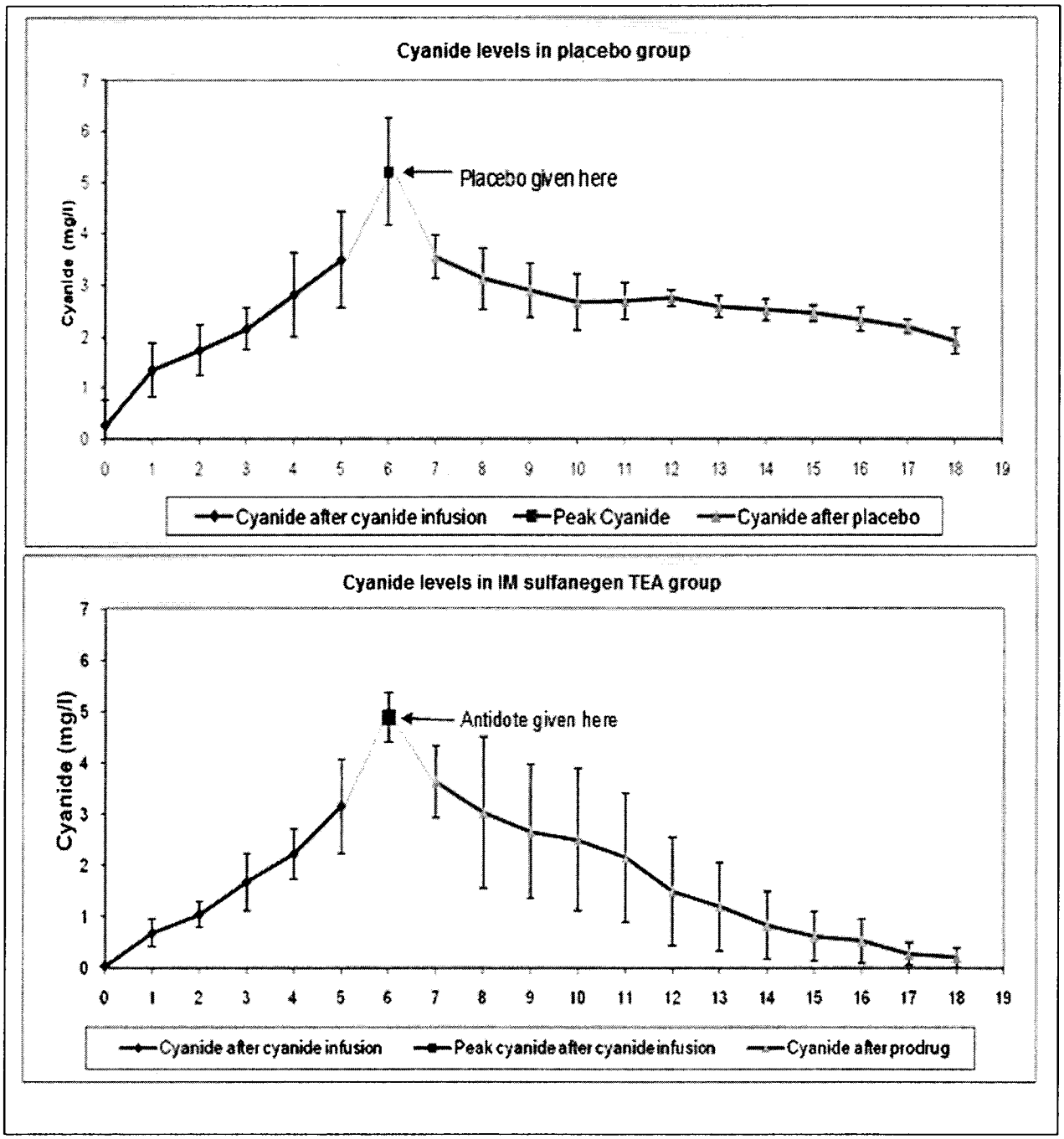
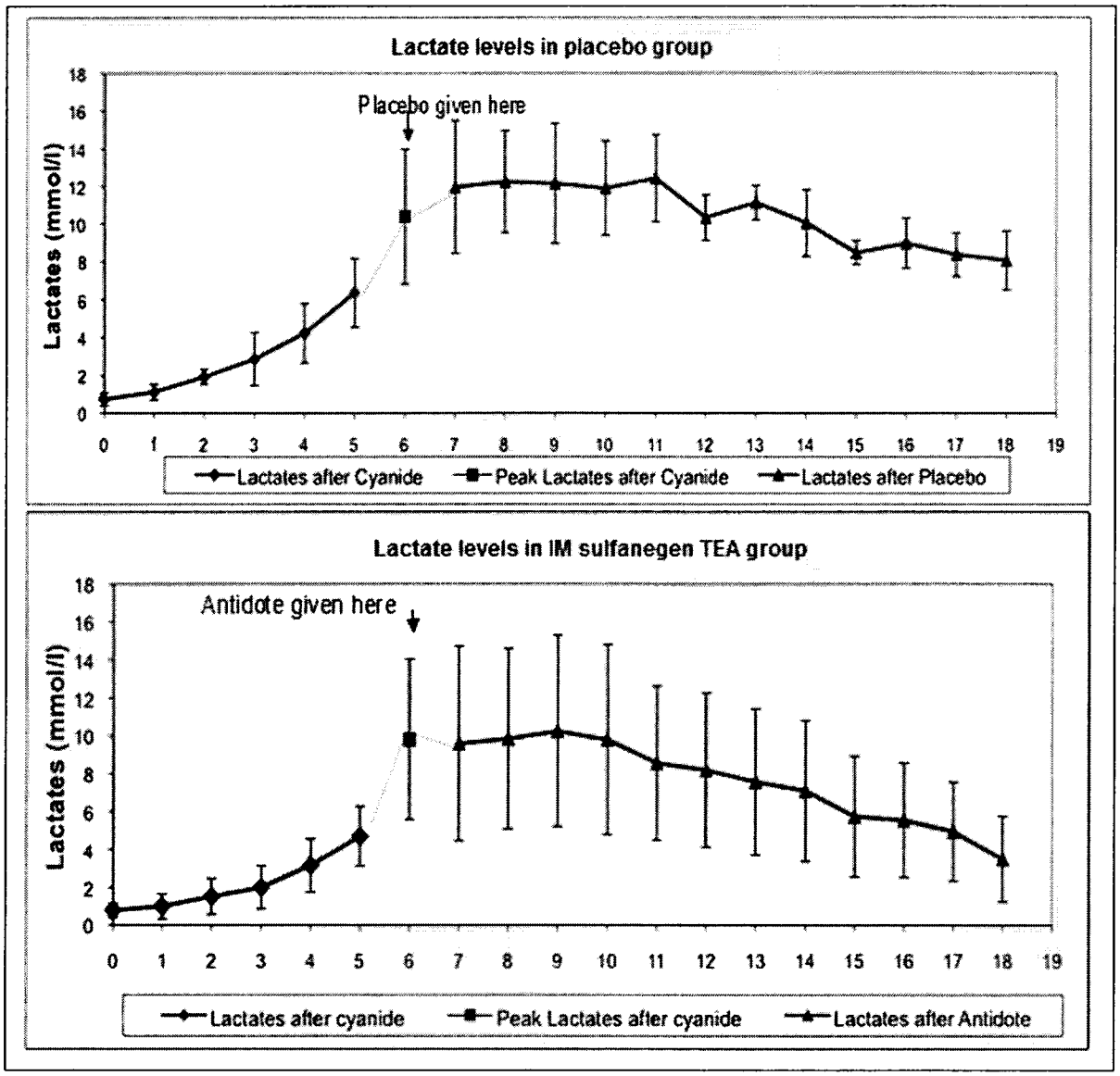

Cyanide levels in placebo group
Cyanide (mg/l)
Placebo given here
Cyanide after cyanide infusion
Peak Cyanide
Cyanide after placebo
Cyanide levels in IM sulfanegen TEA group
Cyanide (mg/l)
Antidote given here
Cyanide after cyanide infusion
Peak cyanide after cyanide infusion
Cyanide after prodrug

Figure 8b


Lactate levels in placebo group
Placebo given here
Lactates (mmol/l)
Lactates after Cyanide
Peak Lactates after Cyanide
Lactates after Placebo
Lactate levels in IM sulfanegen TEA group
Antidote given here
Lactates (mmol/l)
Lactates after cyanide
Peak Lactates after cyanide
Lactates after Antidote