Chapter 11
Transport Medications:
Pharmacology And Protocol Of Administration

Medications administered during transport and the induction of hypothermia in cryonic suspension patients have the objectives of:

1) Protecting against or minimizing re-perfusion injury which may result from restoration of circulation following ischemia associated with pronouncement of legal death.

2) Minimizing the effects of agonal and CPR-associated hypoperfusion and inadequate gas exchange.

3) Protecting against or minimizing the effects of hypothermia during CPR, and cold ischemia during subsequent air transport or other shipment.

4) Supporting perfusion pressure by maintaining vascular tone and/or replacing depleted circulating volume.

5) Protecting against the return of consciousness during cardiopulmonary support.

What follows is a list of the medications with dosage, the route of administration, and purpose of the medication as it is employed in the transport of cryonic suspension patients. Medications are to be given in the order listed below:

Potassium Chloride, 1 mEq/kg, is an electrolyte. Potassium chloride is administered by rapid IV infusion to reduce cerebral metabolic demand by eliminating electrical activity and reducing brain energy expenditure in "pumping" potassium.

Sodium Pentobarbital (Sagatal, Nembutal, Diabutol), 33 mg/kg, is a general anesthetic. Pentobarbital is administered intravenously as a bolus at the start of the resuscitation effort to eliminate the risk of the patient regaining consciousness and experiencing discomfort during cardiopulmonary support. It also reduces brain metabolism to protect the brain's energy stores.

Do not draw up this medication more than one hour in advance of need, since it will rapidly degrade the rubber seal on the syringe. The solubility of pentobarbital is dependent upon the pH; it must not be diluted in other solutions or medications prior to administration. It should be given as a "push" or bolus through the medication port of the IV solution administration set. Never dilute pentobarbital or give it with any other agent or vehicle solution.

Deferoxamine HCl (Desferal), 2 g IV push, is an iron-chelating agent. Deferoxamine combines with free iron (ferritin, hemosiderin) and renders it chemically non-reactive. There is substantial evidence that production of free iron during ischemia is a major cause of free radical-mediated ischemic injury. Desferal chelates the iron and thus prevents subsequent cascades of free radicals which iron can generate.

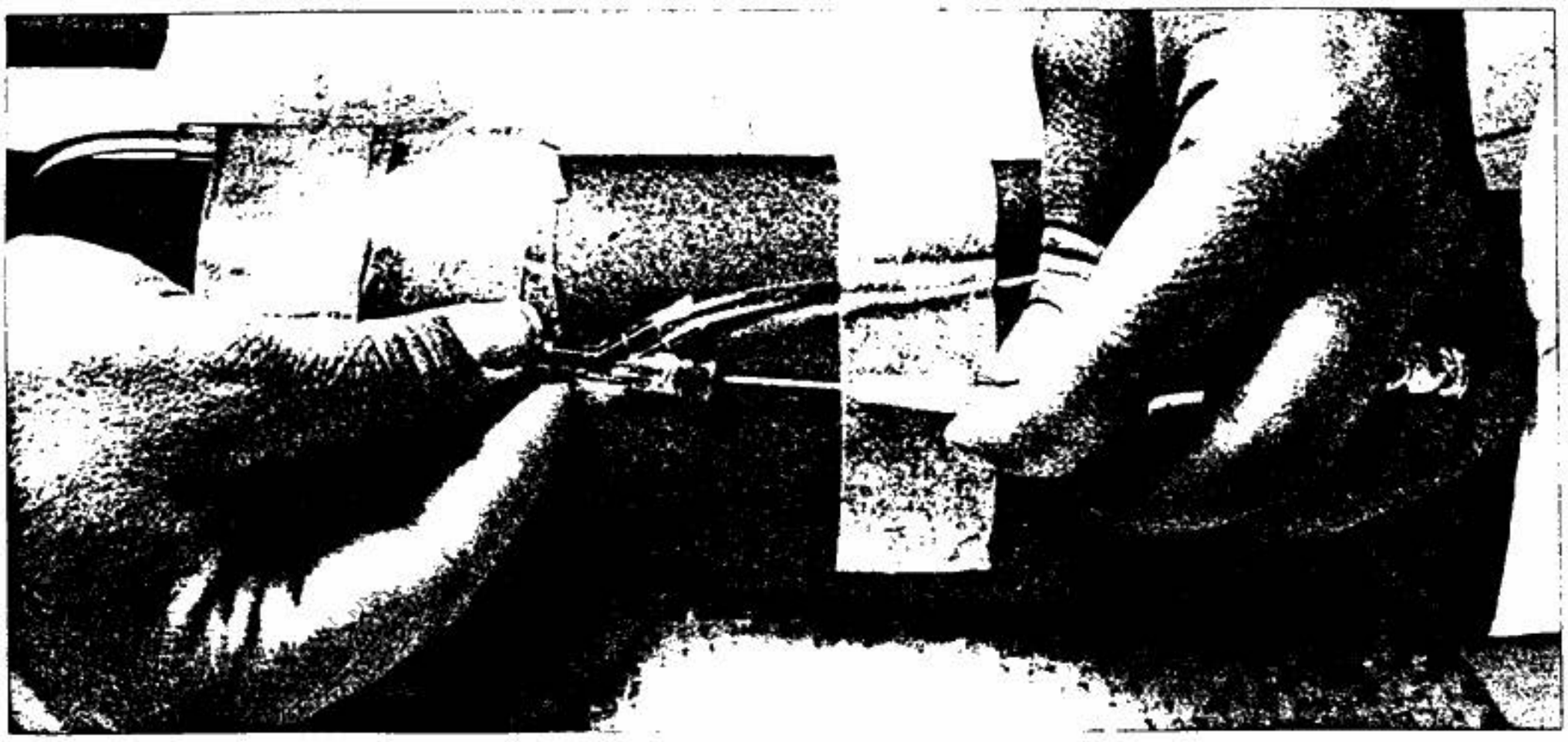

Figure 11-1: *"Piggybacking" a second administration set onto the medication addition port of a primary solution administration set.*

Nimodipine (Alcor supplied), 10 *micro*grams/kg IV push followed by 60 *micro*grams/kg/hr by continuous IV infusion. Nimodipine is a calcium channel blocker used to minimize or prevent injury resulting from calcium influx into cells during hypoxia or ischemia.
Caution: This product is supplied by Alcor in the amount of 5 *milligrams*.

During ischemia or hypoxia, the electrolyte balance of the cells becomes disturbed because there is insufficient energy available to the cells to power the electrolyte pumps which are present in the cell membranes. Normally, the concentration of calcium present outside the cell is 10,000 times greater than that present inside. Initial imbalances (primarily in the concentration of sodium and potassium in the cells) result in the opening of the calcium channels. Once these channels are open, large amounts of calcium enter the cells from the blood and other extracellular fluid. This influx of calcium deranges cell metabolism and results in the production of very damaging compounds and free radicals which directly degrade cell structure and cause the release of structure-destroying enzymes which exacerbate the problem, in part by opening up the membrane to even more calcium influx.

Nimodipine helps to close off or inhibit the flow of calcium through the calcium channels and thus block the secondary damaging effects of calcium.

Calcium channel blockers tend to have a fair amount of specificity for a given tissue type. In both laboratory and clinical trials, the most effective calcium entry blocker for the ischemically injured *brain* is **nimodipine.**

Nimodipine is a powerful drug that is pharmacologically active in microgram per kilogram quantities. It is completely insoluble in water and only poorly soluble in ethanol or propylene glycol. A vehicle solution consisting of 25% (v/v) each of ethanol, propylene glycol, polyethylene glycol 400, and water is used to dissolve the drug for administration.

Nimodipine is also somewhat sensitive to white light and, decomposes to inactive degradation products upon extended exposure to white light. Thus, nimodipine should be shielded from light until it is to be given by leaving it within the foil over-wrap. Do not draw up the medication until it is to be administered.

The procedure for preparing nimodipine for administration is as follows:

Packaging and Preparation Procedure

Each amber ampule of nimodipine contains 5 mg of the drug dissolved in a vehicle solution and ready for administration.

Nimodipine should be drawn up as close to the time of use as possible and kept foil wrapped since it is photosensitive and since it may be absorbed into the plastic and rubber of the administration equipment. Use the following method to draw the medication up and administer it:

1) After determining the dosage, remove the ampule from the foil over-wrap and draw up the required amount of medication. Attach an 18 gauge 1½" needle to the syringe.

2) Administer the medication. Do not leave medication in the syringe for an extended period of time, as the vehicle solution will react with the plunger/syringe barrel.

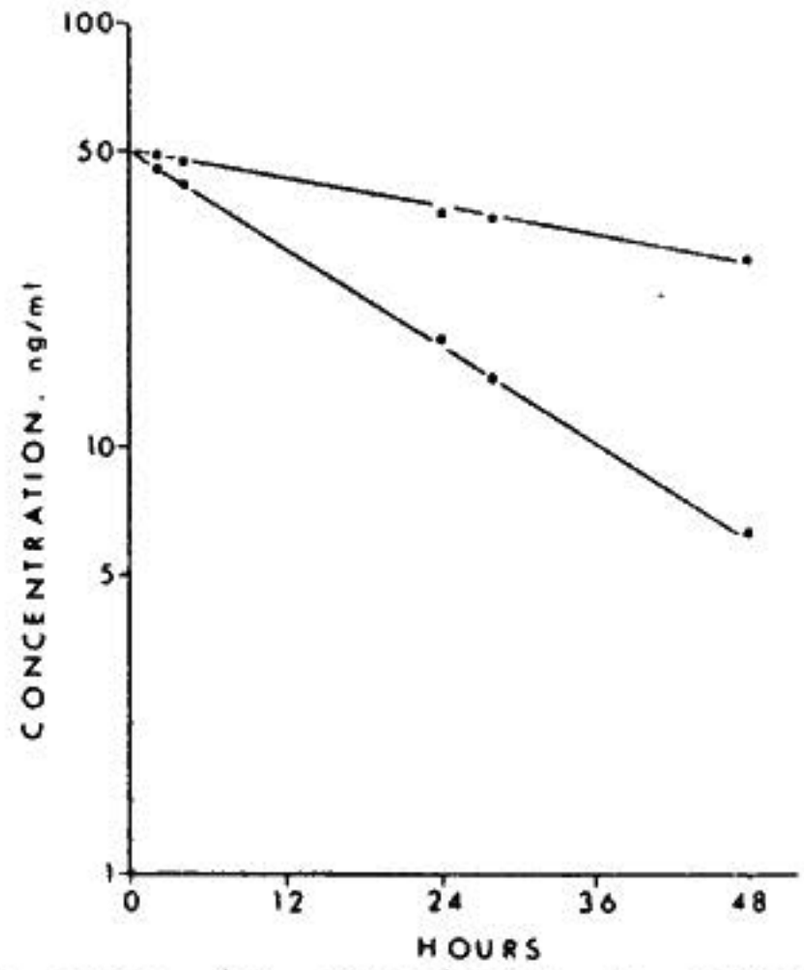

Figure 11-2: *Degradation curve for nimodipine in vehicle solution upon exposure to white light (■) and ultraviolet light (•).*

Diltiazem HCl (Alcor supplied), 300 *micro*grams/kg, is a calcium channel blocker for field use as an alternative to nimodipine. Diltiazem is a cardiospecific calcium channel blocker which has been shown to have some cerebroprotective effects as well.

Diltiazem is freely soluble in water and can be dissolved in normal saline or other water-based vehicle solution. It is hygroscopic and temperature sensitive and must be stored *desiccated and under refrigeration until use is anticipated.*

Packaging and Preparation Procedure

Diltiazem is supplied by Alcor as a powder in nonsterile 5 cc amber ampules. It must be sterilized by filtration through a 0.20 micron filter after being dissolved in an appropriate vehicle solution.

After dissolving the drug in a vehicle solution such as normal saline, draw it into a syringe and attach a Millex 0.2 micron filter (take care to keep the downstream, "needle end" of the Millex *sterile*). Attach an 18 gauge needle to the tip of the Millex and prime the Millex and needle with medication solution. The medication may then be injected into the patient and the Millex will filter sterilize it as it is administered. See the drawing below for details.

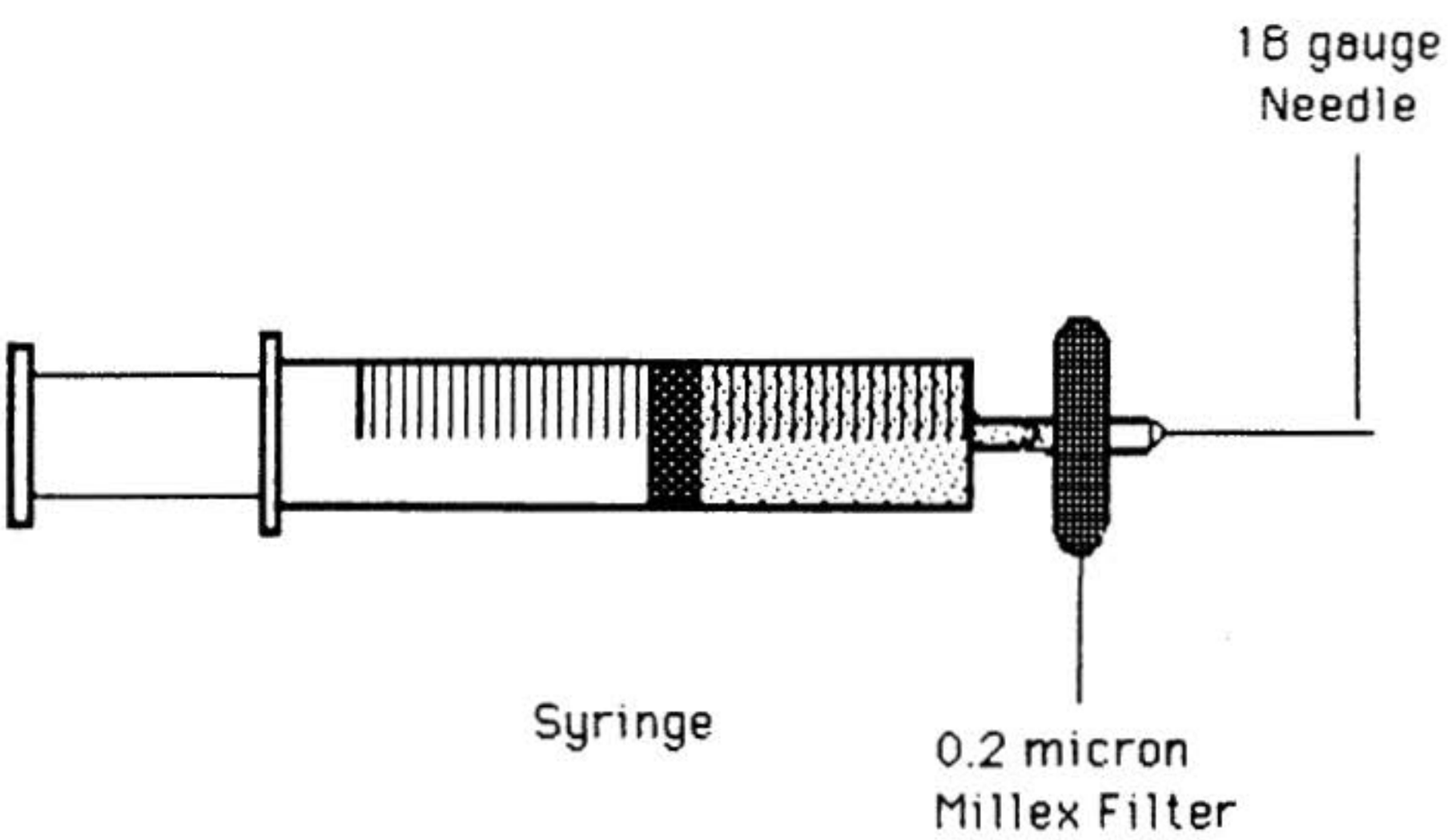

Figure 11-3: *Assembly for in-line filter sterilization of diltiazem during administration.*

Sodium Citrate, 120 mg/kg, is a calcium chelator. It chemically reacts with calcium in a way that renders the calcium chemically nonreactive. Sodium citrate reduces serum calcium concentrations and helps minimize reperfusion injury due to calcium influx into ischemically compromised cells.

Tromethamine (THAM), 252 mg/kg, is a potent organic buffer. The initial dose of tromethamine is 100 cc of a 0.3 M solution given intravenously by rapid infusion at the start of CPR, followed by slow infusion of the remaining 400 cc over the following 2 to 3 hours.

A buffer is a chemical compound which, when present in solution, resists change in the acidity or alkalinity of the solution. After a period of ischemia, or reduced gas exchange, or tissue perfusion, blood and body fluids shift from being slightly alkaline (normal blood pH is 7.4) to being moderately acidic (pH 6.6 to 7.3). For the purposes of this discussion, pH may be defined as a measure of the acidity or alkalinity of a solution (the hydrogen ion concentration). Low pH is damaging to cells and promotes the release of structure-destroying enzymes from intracellular

organelles. It also promotes blood clotting and tissue swelling and causes clumping of red blood cells resulting in blockage of capillaries and further reduction in tissue perfusion.

Tromethamine is used to counteract the organic acids produced by metabolism in the absence of adequate oxygen and nutrients and thus to restore the pH of blood and body fluids to normal or near normal levels.

It is very important to understand that the pH scale of measurement is a logarithmic one. Thus, when the pH changes by 0.3 units, the hydrogen ion (H^+) concentration (acid concentration) doubles or halves:

pH	H^+ ion concentration
7.4	Normal
7.1	Double
6.8	Double Again (4 x Normal)

An examination of the table above readily reveals why problems occur during cardiac arrest or reduced perfusion. What appear to be small changes in pH numerically are in reality massive alterations in the concentration of ions. When ion concentration increases, pH decreases.

Sodium Heparin (Heparin), 420 I.U./kg is an anticoagulant. Heparin is given as a bolus by administration through the medication addition port of the IV solution administration set. It is important to check the strength of the heparin preparation being used before administering it, as it can vary widely depending upon the intended use i.e., dilution in an IV, direct administration, and so on). The usual strength employed in cryonic suspension operations is 10,000 units/ml.

Heparin is administered to *prevent* coagulation of blood not only during initial stabilization and external cooling, but also during subsequent air shipment of the patient. This is important, because blood will normally clot if it is not kept in constant motion, even within the blood vessels of the body. Obviously, after external cooling is complete, artificial circulation will be discontinued to facilitate air transport and, in the absence of anticoagulation, clotting would normally be expected to occur.

It should be noted that the effectiveness of heparin is to a great extent dependent upon proper control of pH. If the pH drops significantly below 7.0 (more than 0.3 units), heparin will start to degrade and inactivate. Adequate control of pH is thus essential in order to achieve and maintain anticoagulation.

Note: *Heparin will not reverse clotting. It only prevents it.*

Chlorpromazine (Thorazine, Largactil), 3 mg/kg IV push, is a membrane stabilizer which has shown effectiveness in reducing both warm and cold ischemic injury. The mechanism of action is not known. Chlorpromazine is also a major tranquilizer.

Methylprednisolone Sodium Succinate (Solu-Medrol), 1 g by slow IV injection. Methylprednisolone is a corticosteroid which acts to stabilize cell membranes during ischemia and hypothermia. It must be administered slowly, over a period of 3 to 5 minutes.

20% **Mannitol (Osmitrol)**, 2 gm/kg, is a sugar which is used to inhibit cell swelling and in particular to control cerebral edema. It is administered by continuous intravenous infusion over the first 60 to 90 min. of cardiopulmonary support. *Do not spike this bottle until needed.*

Mannitol is an effective osmotic or "water binding" agent. Because it cannot freely pass through cell membranes, it is effective at attracting and holding water in the extracellular spaces, thus preventing cell swelling. Cell swelling is a normal response to hypoxia, ischemia, and tissue injury. The brain, because it is encased in a rigid, bony shell (the skull), is particularly susceptible to the effects of tissue swelling. If brain swelling occurs, the pressure inside the skull will increase, reducing blood flow. Further swelling will then result from decreased blood flow, and a vicious cycle is set up which ultimately results in total inhibition of blood flow to the brain.

Mannitol acts to transiently prevent and even to reverse brain swelling, providing that some blood circulation to the brain is still intact. Mannitol is also a highly effective diuretic (promotes urine formation) and may (although this is very unlikely, due to low perfusion pressure) result in urine production during transport.

An added benefit to the use of mannitol during Transport is its free radical scavenging ability.

Redissolving Mannitol

Carefully examine the bag or bottle of mannitol for the presence of crystals as long in advance of use as possible. If crystals are present in a *bottle* of mannitol, they may be redissolved by warming the bottle in a double boiler or on a coffee warming plate. (Never use a true hot plate, lest the bottle explode). Once the mannitol is redissolved, the bottle should be kept in a warm place or crystallization can recur. Bottles of mannitol may also be heated*very cautiously* in a *microwave.* Great care must be taken to avoid overheating the contents and rupturing the bottle. The procedure for rewarming sealed bottles in the microwave is as follows:

1) Remove the wire hanger ring from the bottom of the bottle. (Retain it as you will need to put it back on when the procedure is completed.)

2) Place the bottle on its side in the center of the cavity of the oven with the top (neck) pointing towards the rear of the oven.

3) Close the door and activate the oven for 15 seconds.

4) Open the oven and check the bottle temperature.

5) Repeat steps #3 and #4 above until the bottle is almost too hot to handle. *Do not try to boil the liquid inside!*

6) Using a paper towel, remove the bottle from the oven and invert repeatedly until the crystals have all dissolved. Reheat the bottle carefully as often as necessary to maintain a "hot to touch" temperature.

Bags of mannitol may be rewarmed by placing them (within their outer, protective wrap) in water that is just under boiling temperature, or with a microwave, using the following technique:

1) Remove outer, protective bag.

2) Place container in the center of the microwave oven cavity.

3) Heat bag for 30 seconds and evaluate for temperature.

4) Repeat step #3 until bag is very hot to touch.

5) Remove bag from oven using paper towel and repeatedly invert until crystals dissolve.

Metocurine (Metubine Iodide), 0.07 mg/kg is a muscle-paralyzing agent. Metocurine is administered intravenously as a bolus via the medication addition port on the solution set. Metocurine is a synthetic derivative of curare, the South American arrow poison used by South American Indians to paralyze prey. It is used to inhibit the shivering which can occur as a response to external cooling.

Shivering increases metabolic demand, consumes valuable cellular energy reserves, and results in production of additional metabolic waste products, further exacerbating acidosis. While not all suspension patients will respond to the induction of hypothermia by shivering, some will. Such shivering may consist solely of action by slow-twitch muscle fibers, which is not readily noticeable. Thus, it is important to protect against the possibility of shivering by administering an agent such as metocurine which inhibits the action of voluntary muscle fibers.

Gentamicin Sulfate (Garamycin, Garamicina), 1 mg/kg IV push. Gentamicin is an aminoglycoside antibiotic which is primarily effective against gram negative bacteria. Gentamicin is used to prevent bacterial overgrowth during cooling and transport of the patient.

Trimethoprim and Sulfamethoxazole (Bactrim), 160 mg Trimethoprim and 800 mg sulfamethoxazole by slow IV infusion. Bactrim is a synthetic antibacterial combination product used to prevent bacterial overgrowth during cooling and transport of suspension patients. Bactrim is effective against a range of both gram positive and negative bacteria.

Bactrim *must* be given by slow IV infusion. It may be added to the **Dextran-40** or the mannitol immediately before they are administered.

Erythromycin (Erythrocyn), 1 gm for adults, 500 mg for children under 12 years of age. Erythromycin is a broad spectrum antibiotic which should be administered slowly by intravenous infusion in a minimum of 20 cc of sterile water for injection. Erythromycin is supplied as a powder and must be dissolved in water prior to administration. It is very important that the erythromycin not be dissolved in any agent other than sterile water for injection to which no preservatives or other agents have been added. Failure to observe this precaution will result in the formation of a viscous gel that cannot be withdrawn from the container. *Note: Erythromycin is to be used only as an alternative to Bactrim/Gentamicin where sensitivity to the latter is known to exist.*

* * *

A Note on Transport Antibiotics:

Antibiotics such as bactrim, gentamicin, and erythromycin are given in order to prevent bacterial overgrowth in the gut, respiratory tract, and circulatory system of the patient during transport. Patients experiencing legal death remote from cryoprotective perfusion facilities will require lengthy HLR-supported external cooling and air shipment packed in ice. The time delays imposed by these logistic constraints offer the opportunity for overgrowth of microorganisms (in particular, cold anaerobes: organisms which can proliferate in the cold). A broad spectrum antibiotic is required to guard against this possibility.

At first glance, the antibiotics listed above would not seem to be the optimum choice for broad spectrum antibacterial activity. The penicillins or cephalosporins would be better candidates because of the wider range of organisms whose replication they can inhibit. Unfortunately, penicillin, cephalosporins, and most other antibiotics are also effective at promoting cold-associated clumping or agglutination of red blood cells. Bactrim, gentamicin, and erythromycin are the only antibiotics known to be free of this effect, hence they have been selected for use in transport operations.

* * *

Dextran-1 (Promit), 1.5 g, which is given IV push, is an allergy-blocking agent used to prevent a possible anaphylactic reaction to Dextran-40. The clinical dextrans are produced by microorganisms in culture, and in fact also are produced by microorganisms which live in the human gut. Thus, a significant fraction of the population is at risk of severe anaphylactic or allergic reaction when Dextran-40 is administered IV. To prevent such a reaction, *Promit should always be administered before Dextran-40 is given.* Promit binds to and locks up the sites on antibodies which would normally react with Dextran-40 molecules to form immune complexes capable of provoking an allergic reaction.

Administration of Dextran-40 must begin within 15 minutes of the administration of Promit. If a longer period of time has elapsed between the administration of Promit and the start of the Dextran-40 infusion, the Promit must be readministered. Promit must never be admixed or diluted with Dextran-40 before being given. Promit should ideally be given 1 to 2 minutes prior to the start of the Dextran-40 infusion.

6% **Dextran-40 in normal saline (Gentran, Rheomacrodex)**, 200 cc to 500 cc, is a plasma expander and inhibitor of cold agglutination. Dextran-40 is administered slowly over a 60 to 90 minute period with a solution administration set. Administration of Dextran-40 should not be undertaken until after completion of the infusion of mannitol and tromethamine. It should begin immediately after the administration of Dextran-1 (see above).

Dextran-40 is an oncotic agent: a compound which is effective in holding water in the vascular (blood compartment) space and preventing the development of fluid accumulation between the cells (interstitial edema). It is also effective at reducing the likelihood of cold agglutination during hypothermia.

50% **Dextrose in Water** may be given as needed to acutely adjust blood sugar. Each 2 cc of 50% dextrose will raise the blood sugar of the average 72 kg patient by 1 mg/dL. Dextrose is the fuel on which most body cells operate. Dosage should be carefully titrated to avoid "overshoot" since serum concentrations of dextrose in excess of 70

mg/dL have been associated with added cerebral injury during CPR. (For details on administration, see page 5-9)

5% Dextrose in Water (D5W), may be given prn by slow IV infusion to support blood glucose during transport. Marked hypoglycemia can occur during transport and cooling of the patient (See above).

Streptokinase (Streptase), 30,000 IU/kg, given IV as a bolus. Streptokinase is a fibrinolytic (clot dissolving) agent to be used only in patients who have experienced 1 or more hours of ischemia in the absence of cardiopulmonary support or transport medications. The use of streptokinase is speculative and has not been documented as effective in cryonic suspension procedures. It is not provided in Alcor kits due to its high cost and the need for refrigeration. Streptokinase may be obtained from the hospital pharmacy. If this agent is needed, call ASC for instructions/support.

Aluminum Hydroxide/Magnesium Hydroxide (AH/MH) (Maalox), 200 cc, is a stomach antacid. AH/MH should be given via gastric tube after the administration of those transport medications which are given as a bolus. AH/MH is a direct neutralizer of gastric hydrochloric acid. Neutralization of gastric HCl which is already present in the stomach at the time of cardiac arrest is critical in protecting the gastric mucosa from ulceration during subsequent hypothermic transport, TBW, and cryoprotective perfusion.