CHAPTER 11

PREPARING AND ADMINISTERING THE T3 STUDY DRUG

11.1 STUDY DRUG INFUSION

The dose of T3 study drug will be 0.8 mg/kg (not to exceed 80 mg). One-third of the total dose (not to exceed 20 mg) is to be administered as an IV push bolus and the infusion dose over 90 minutes. The Nomogram Dosing Chart (Exhibit 11-1) should be used to determine the TOTAL DOSE of T3 study drug, the BOLUS DOSE, the INFUSION DOSE and the corresponding DRIP RATE. [NOTE: It is recommended that only one vial of T3 study drug be reconstituted when the total dose of T3 is 50 mg or less (the remaining vial can be used in case of preparation error or other problems)].

FDA regulations require that the amount of experimental study drug given to the patient be documented in the medical record. There are two required procedures to address this issue in T3. First, since the T3 study drug is weight dependent, the patient's exact weight (in kilograms) at the time of entry into the study, should be documented in the medical record. Second, the total T3 study dose (the amount to be injected as a bolus, plus the amount to be infused over 90 minutes) should be recorded in the medical record. For example:

1. Patient weight at randomization _____kg.
2. Total T3 dose _____mg.
3. Bolus dose _____mg.
4. Infusion dose _____mg.

Five points in particular need to be emphasized. First, the T3 study drug infusion must be started as soon as possible after patient eligibility has been established and informed consent obtained. The appropriate medication kit (based on the Treatment Allocation Mailer Assignment) should be obtained and readied for preparation. Any necessary equipment or supplies not provided in the medication kit should be obtained immediately from the Clinical Center's supplies.

Directions for preparing and administering the infusion are enclosed in each kit (Exhibit 11-2). Preparation of the T3 study drug should begin immediately upon completion of patient eligibility and consent. **[NOTE: The T3 drug solution can be used for up to eight hours following reconstitution when it is stored between 36-86EF or 2-30EC. Do not store any remaining unused portion for future use.]**

Second, the T3 study drug lyophilized powder is subject to formation of foam and bubbles during reconstitution. Extreme caution must be exercised to avoid this problem. Slowly add the Sterile Water for Injection, USP (preservative free) and the only solution to be used for 1:1 dilutions) to the vial of lyophilized powder, directing the stream of diluent into the lyophilized cake. Swirl and/or invert the vial **gently** to aid reconstitution. ***DO NOT SHAKE***. Shaking or other agitation will cause foam and bubbles to form. Slight foaming when reconstituting is not uncommon. If foam or bubbles do form, place the vial(s) upright on a flat surface and let stand undisturbed for several minutes. This is usually sufficient time to allow for the dissipation of any large bubbles. Care must also be exercised when transferring the T3 study drug solution into the IV infusion container, to again eliminate the problem of foam and bubbles. Forcing, shaking or agitating the solution will cause foam and bubbles. *[NOTE: Do not add any other medications to syringes or infusion bags containing the T3 study drug.*]

Third, caution must be exercised over the choice of an IV pump. Although any IV pump, Harvard pump, or radiographic injector can be used, the drop-dependent devices must be closely monitored. The IVAC type infusion is recommended. The drug may increase the drop size, thereby speeding up the rate of infusion beyond what is expected. If a drop counting device is used for the T3 study-drug infusion, closely observe the actual rate of infusion and adjust accordingly. Also, as mentioned above, radiographic injectors may cause problems with the T3 study drug infusion. Aspirating the drug into the injector may prove

difficult and can result in delays in starting the infusion. Injector type devices may also present significant dead space depending on the tubing used. Each Clinical Center, Satellite or Co-Equal site intending to use an injector should measure this volume and if found to be significant, make plans to compensate for the problem.

Fourth, the T3 study-drug infusion should be administered through a separate IV line using a heparin lock.

Fifth, the bolus dose should not be administered using a filter needle and in-line filters should not be used while infusing the T3 study drug. Use of certain in-line filters as part of the intravenous delivery system may lead to substantial reductions in the amount of study drug delivered to the patient. This phenomenon appears to be related to filter component material rather than pore size or flow rate. Since in-line filters are not required during T3 study drug administration, their routine use should be avoided.

11.2 EVALUATION AND MANAGEMENT OF SIDE EFFECTS AND ADVERSE REACTIONS WITH rt-PA

Other than bleeding, no adverse effects of rt-PA are expected in T3 patients. No adverse effects of administration of t-PA in animals have been observed. Since t-PA has been indistinguishable from human intrinsic t-PA, the possibility of allergic responses is not anticipated. Nevertheless, routine anti-allergy therapy should be available in the unlikely event of such occurrence.

Should any (unexpected) allergic reactions occur, the rt-PA being infused must immediately be discontinued. The administration of diphenhydramine (Benadryl) 25-50 mg (slow IV over 5-10 min) or chlorpheniramine maleate (Chlortrimeton) 10 mg (slow IV over 5-10 min) and 60 mg methyl prednisolone (Solu-Medrol) IV are recommended. Standard treatment of anaphylaxis, including epinephrine, intravenous fluids, and establishment of a proper airway with adequate oxygenation, should be administered as required by the situation.

Should severe febrile reactions occur (sustained fever of 103°F or 39°C or greater), acetaminophen (Tylenol) 325-650 mg orally or propoxyphene (plain Darvon) 65 mg orally every 6 hours may be given as the infusion continues.

Reperfusion-related side effects during the acute study period are limited to ventricular tachyarrhythmias (frequent VPCs, short runs of automatic idio-ventricular rhythm, self-limited or sustained ventricular tachycardia, or ventricular fibrillation) or bradyarrhythmias (sinus bradycardia, high grade atrioventricular block) with or without hypotension. The incidence of sustained VT/VF has ranged from 0 - 10% and in all reported instances these arrhythmias have responded very promptly to DC cardioversion and/or antiarrhythmic drugs. Bradyarrhythmias have been treated successfully with intravenous atropine, fluids and/or temporary transvenous pacing. Sustained ventricular tachycardia or ventricular fibrillation will be rapidly treated by synchronized DC cardioversion. Bradyarrhythmias, if associated with observed or potential symptomatic or hemodynamic instability, will be treated with atropine sulfate and/or insertion of a temporary pacemaker. Transvenous pacing will be continued for 72 hours, or longer as needed.

A mild fibrinolytic state may develop. However, fibrinogen levels can be expected to remain above 150 mg/Dl in the majority of patients (as evidenced by coagulation studies performed during TIMI Phase I and Phase II) and thus an excess of bleeding problems related to the rt-PA itself are not anticipated.

All T3 patients will receive standard IV heparin therapy and will, therefore, be at risk of bleeding complications, particularly in patients undergoing early catheterization.

All sites of vascular invasion will be scrutinized every two hours during the acute study period (at least during the first 24 hours). In the unlikely event that hemorrhage should occur during the acute drug administration, it is recommended that the study drug be immediately discontinued. Should this occur during the 24-hour period following

initiation of the study drug infusion, heparin should be discontinued and reversed with protamine sulfate in the standard manner. Blood specimens should be drawn to measure prothrombin time (PT), partial thromboplastin time (PTT), thromboplastin time (TT), fibrinogen, and complete blood count (CBC).

Should hemorrhaging occur, epsilon aminocaproic acid (Amicar) which acts as an effective inhibitor of fibrinolysis (it inhibits the conversion of plasminogen to plasmin and will also inhibit the activity of plasmin) should be given IV in a dose of 5 gm (in 5% dextrose) slowly during 30 minutes. Usually a single dose is adequate. If there is evidence of continued fibrinolysis, repeat doses of 1 gm every two hours may be given. Administration of more than 30 gm/24 hrs is not recommended. While the Amicar is being infused, cryoprecipitate (4-6 bags) [or, with attention to the patient's volume status, fresh frozen plasma (3 bags)], should be administered intravenously. Packed red blood cells, or whole blood and crystalloid should be administered as clinically necessary. Amicar should not be given in the presence of disseminated intravascular coagulation or in the presence of gross hemorrhage in the upper tract of the genito-urinary system since it may predispose to clot formation in the renal pelvis.

Specific therapy should be administered according to site of bleeding (e.g., antacids and/or H-2 receptor blocker [Cimetidine] for upper gastrointestinal hemorrhage).

CBC will be monitored at least every 12 hours during the first 24 hours following intervention, or more frequently, as clinically indicated. Stool, urine and vomitus specimens will be tested for occult blood. Frequent clinical assessment and examination will be performed by the investigator to assess potential internal hemorrhage. Major vascular catheter entry sites should be minimized and protected with sheath-introducers to tamponade the site for approximately 24 hours (by the end of which the fibrinolytic state should return to baseline). Vascular puncture sites will be treated with compression dressings.

All untoward complications will be noted, and life-threatening hemorrhagic or allergic complications or any highly unusual adverse effect will be reported immediately to the Coordinating Center and the Program Office. If the complication is considered serious or alarming, the investigator should complete and forward to the Program Office a special report using FDA Form 1639, Adverse Reaction Report. Please refer to Chapter 5, Adverse Event Reporting, of the Manual of Operations for more detail on this topic.

EXHIBIT 11-1

NOMOGRAM DOSING CHART

When prepared as directed, the final concentration of T3 is: **1 mg/1 ml**

1. Reconstitute the vial(s) with 50 ml of sterile water (Conc. = 1 mg/ml)
2. Withdraw and administer the "Bolus Dose"
3. If total dose is 58 mg or less, add an equal volume of either normal saline or 5% dextrose. Withdraw the "Infusion Dose," add it to the infusion bag then add volume of either normal saline or 5% dextrose
4. Infuse at the appropriate drip rate

Wgt (Kg)	Total Dose (mg)	Bolus (mg)	Infusion Dose (mg)	Additional Diluent (ml)	Drip Rate (ml/hr)
40	32	11	21	21	28
41	33	11	22	22	30
42	34	11	23	23	30
43	34	11	23	23	30
44	35	12	23	23	30
45	36	12	24	24	32
46	37	12	25	25	34
47	38	13	25	25	34
48	38	13	25	25	34
49	39	13	26	26	34
50	40	13	27	27	36
51	41	14	27	27	36
52	42	14	28	28	38
53	42	14	28	28	38
54	43	14	29	29	38
55	44	15	29	29	38
56	45	15	30	30	40
57	46	15	31	31	42
58	46	15	31	31	42
59	47	16	31	31	42
60	48	16	32	32	42
61	49	16	33	33	44
62	50	17	33	33	44
63	50	17	33	33	44
64	51	17	34	34	46

EXHIBIT 11-1 (Continued)

NOMOGRAM DOSING CHART

Wgt (Kg)	Total Dose (mg)	Bolus (mg)	Infusion Dose (mg)	Additional Diluent (ml)	Drip Rate (ml/hr)
65	52	17	35	35	46
66	53	17	36	36	48
67	54	18	36	36	48
68	54	18	36	36	48
69	55	18	37	37	50
70	56	18	38	38	50
71	57	19	38	38	50
72	58	19	39	39	52
73	58	19	39	39	52
74	59	19	40	0	27
75	60	20	40	0	27
76	61	20	41	0	27
77	62	20	42	0	28
78	62	20	42	0	28
79	63	20	43	0	29
80	64	20	44	0	29
81	65	20	45	0	30
82	66	20	46	0	31
83	66	20	46	0	31
84	67	20	47	0	31
85	68	20	48	0	32
86	69	20	49	0	33
87	70	20	50	0	33
88	70	20	50	0	33
89	71	20	51	0	34
90	72	20	52	0	35
91	73	20	53	0	35
92	74	20	54	0	36
93	74	20	54	0	36
94	75	20	55	0	37
95	76	20	56	0	37
96	77	20	57	0	38

EXHIBIT 11-1 (Continued)

NOMOGRAM DOSING CHART

Wgt (Kg)	Total Dose (mg)	Bolus (mg)	Infusion Dose (mg)	Additional Diluent (ml)	Drip Rate (ml/hr)
97	78	20	58	0	39
98	78	20	58	0	39
99	79	20	59	0	39
100 AND OVER	80	20	60	0	40

EXHIBIT 11-2

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T3)

PREPARATION AND ADMINISTRATION SUMMARY

[T3 Study Drug, 50 mg per vial]

A. PREPARATION:

1. Use only Sterile Water for Injection, USP (preservative free) to reconstitute the T3 study drug.

2. Slowly add 50 ml of Sterile Water to each T3 study-drug vial needed (one in both, depending on the dose). Do not let the vacuum in the vial draw the water rapidly from the syringe. Direct the stream of water into the lyophilized powder cake. A 50 ml syringe and an 18 gauge, 1½" needle are recommended for reconstitution and drug transfer.

3. ***DO NOT SHAKE*** the vial to dissolve the powder cake: shaking will cause foaming. Gently swirl and/or invert the vial to aid reconstitution. If foaming occurs, place the vial in an upright position on a flat surface and let stand undisturbed for several minutes. This is usually sufficient time to allow for dissipation of any large bubbles. The concentration of the solution (1:1 dilution) will be **1 mg per 1 ml.**

4. Use the Nomogram Dosage Chart (Exhibit 21-2) to determine the TOTAL DOSE of T3 (based on the patient's weight in kilograms), the BOLUS DOSE, the INFUSION DOSE, and the corresponding DRIP RATE. When transferring the T3 study drug to the IV infusion container, be careful not to shake, agitate or force the T3 drug solution since this may cause the solution to foam.

5. If the total dose of T3 is 58 mg or less:

   a. reconstitute the vial(s) with 50 ml of sterile water (yielding an initial concentration of 1 mg/1 ml).

   b. withdraw and administer the "BOLUS DOSE."

   c. withdraw the "INFUSION DOSE," add it to the infusion bag and then slowly add an equal volume of either normal saline or 5% dextrose (yielding a final concentration of 0.5 mg/1 ml).

   d. gently rotate the IV infusion bag to effect a solution.

   e. infuse at the appropriate "DRIP RATE."

EXHIBIT 11-2 (Continued)

THROMBOLYSIS IN MYOCARDIAL ISCHEMIA (T3)

PREPARATION AND ADMINISTRATION SUMMARY

[T3 Study Drug, 50 mg per vial]

B. ADMINISTRATION

1. The TOTAL DOSE of T3 = 0.8 mg/Kg (not to exceed 80 mg):

   a. Administer one-third of the total dose (not to exceed 20 mg) as an *IV PUSH BOLUS*.

   b. Administer the *INFUSION DOSE* over 90 minutes.

   c. Add 25-50 ml of either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP (preservative free) to the empty IV infusion container and continue infusing at the rate indicated on the Nomogram until the total infusion dose has been administered.

      EXAMPLE: After reconstituting the T3 study drug, the final concentration is 1 mg/1 ml. A patient weighing 80 Kg needs a total dose of 64 mg or 64 ml of the drug solution. One-third of this dose, 20 mg or 20 ml of the drug solution, will be administered as an IV push bolus. The infusion dose, 44 mg or 44 ml of the 1:1 drug solution, will be placed in the IV infusion container and administered over 90 minutes (rate = 29 ml/hr*). When the infusion container is empty, add an additional 25-50 ml of either D5W or NS (preservative free) and continue infusing at the same rate (29 ml/hr) until the entire infusion dose has been administered, i.e., 44 ml.

      *If the total dose of T3 is 58 mg or less, a second dilution of the drug is necessary to facilitate ease of administration. This dilution will yield a solution containing 0.5 mg/ml. Refer to the Nomogram Dosing Chart for instructions.

2. Pumps:

   a. An IVAC or similar pump is recommended.

   b. Drop counting devices must be monitored closely for accurate drip rates.

   c. Harvard pumps and radiographic injectors - use care when drawing the drug solution into the syringe to avoid foaming.

T3 MANUAL OF OPERATIONS

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