Medical Grand Rounds

May 9, 1968

# DILANTIN - Experimental Studies and Clinical Use

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Case 1 [redacted]: [redacted] is a 50 year old man who was in good health until the day prior to admission, at which time, while pushing a truck, he experienced a transient episode of chest discomfort which lasted 4 - 5 minutes before it subsided spontaneously. The morning of admission, he experienced a sudden, severe, oppressive precordial pain radiating into both arms and accompanied by nausea, shortness of breath, and a cold diaphoresis. His distress was unrelenting and brought him to the emergency room.

On admission [redacted]/65), the ECG revealed an acute anterior myocardial infarction. He was initially stable, but while being observed, he developed multifocal PVC's of increasing frequency and finally a slow ventricular tachycardia. He became hypotensive. Restoration of his blood pressure failed to affect the arrhythmia, and he was given I.V. Dilantin (250 mg). Within 3 minutes, a normal sinus rhythm was restored and he was able to maintain his own blood pressure. He was continued on I.M. Dilantin for 5 days (250 mg q. 6 h), and thereafter on oral Dilantin (100 mg tid) without further arrhythmias.

His course was complicated only by a bronchopneumonia which responded to antibiotics. He was discharged on the 37th day, and his convalescence has been uneventful.

Case 2 [redacted]: A 47 year old man was admitted on [redacted]/67 with chest pain of 6 hours duration. The chest pain was accompanied with pain, sweating, nausea, vomiting, and orthopnea. This pain prompted his admission to [redacted]. In 1955 he had had mitral commissurotomy with marked improvement.

BP 130/80; pulse 96/min.; respiration 16/min.; he was having a moderate chest pain; the neck veins were flat; the lungs were clear; an apical diastolic rumble with opening snap was heard; the $P_2$ was accentuated. His ECG revealed an acute inferior myocardial infarction and a sinus rhythm.

Continuous monitoring revealed, at 11:35, 1° AV block which later progressed to 2:1 AV block and 3° AV block. At 11:50, the abnormal AV conduction converted to atrial flutter-fibrillation and many PVC's with coupling. Shortly thereafter, persistent ventricular tachycardia appeared.

Slow I.V. Dilantin started (250 mg at 11:55 - 12:00), suppressed the ventricular tachycardia and reappearance of the atrial arrhythmia. The patient was digitalized and sinus rhythm emerged. The patient was maintained on both Digoxin (0.25 mg daily) and Dilantin (100 mg orally tid) with good result.

Case 3 ([redacted]): A 58 year old was admitted on [redacted]/66 with retro-sternal chest pain of 1 hour duration. The pain was severe in character, radiated to both arms, and was associated with nausea and vomiting. The pain was relieved by morphine. The patient

gave a history of angina pectoris and was hospitalized 1 - 2 years with history suggestive of an acute M.I.

On admission, the patient was in moderate distress. BP 190/110. The neck veins were not distended. The heart was not enlarged. There were no murmurs or gallops. The ECG on admission (8:30) showed an A.V. dissociation with an acute myocardial injury involving the diaphragmatic area. I.V. Dilantin was administered at 9:15 (100 mg), and I.M. Dilantin at 9:50. A 2nd ECG taken at 10:10 revealed normal sinus rhythm and the ST segment regressed to baseline.

The following ECG's revealed evolutionary changes of a diaphragmatic myocardial infarction. Continuous monitoring for 72 hours was started 4 hours after the onset of chest pain, and revealed only two runs of VT of 5 PVC's each, one at 13:30 and the other at 13:47.

Case 4 - [redacted]: A 75 year old man was admitted to the medical service on [redacted]/66 with "black-out spells". In [redacted], 1966, the patient experienced his first "black-out spell", which lasted 30 minutes. He was hospitalized in a local hospital with the diagnosis of 1st degree AV block, left bundle branch block, congestive heart failure, and "idiopathic epilepsy". He was digitalized and maintained on Digoxin (0.25 mg daily). Later, he was started on Dilantin (300 mg daily) with decrease in the number of "black-out spells". In the week prior to admission, the seizures increased in frequency. On the day of admission, he had had several episodes of unconsciousness.

During some of these spells, the patient has had fecal and urinary incontinence, tonic but no clonic movements. These spells occurred suddenly without warning, and lasted seconds to a few minutes. The treating physician noted that during these spells, the pulse was slow, and he referred the patient with a note stating the diagnosis as "chronic myocarditis".

On admission, the pulse rate was 34/min. and regular. The blood pressure was 128/62. The neck veins were not distended; the AP diameter of the chest was increased, and diffuse basilar rales were present. The left border of the cardiac dullness was several centimeters beyond the MCL; a grade ii ejection systolic murmur was heard across the precordium; the $S_1$ was of variable intensity; no atrial sounds or gallops were heard. There was no peripheral edema.

Hemoglobin blood level 16.2 gm per 100 ml; hematocrit 57%; neutrophilic leukocytosis with total white cell count of 15,200 per ml. Platelet count was 665,000. BUN was 28 mg%; serum creatinine 2.7 mg%; fasting blood sugar 111 mg%; normal serum electrolytes; SGOT 54 units per ml; and normal urinalysis. Dilantin blood level was 0.82 mg%.

The electrocardiogram on admission revealed a 3rd degree AV block. Following admission, an intravenous pacemaker was placed in the

R.V. cavity and set at a rate of 72/min., and Dilantin was discontinued. On [redacted]/66, a permanent pacemaker was installed by the surgery department. When last seen on [redacted]/67, the patient was doing well and his pulse rate was 72 per minute and regular.

Case 5 - [redacted]: A 34-year-old obese and hypertensive woman was admitted to the Medical Service on [redacted], 1966, complaining of yellow vision, nausea and vomiting of one week duration. A month prior to admission, she began experiencing paroxysmal nocturnal dyspnea. She was digitalized, and was maintained on 0.50 mg digoxin daily, with daily thiazide diuretic. Three days prior to admission, she experienced episodes of palpitations which increased in frequency and duration. The last episode lasted 20 minutes; it was associated with shortness of breath, rapid heart rate, and dizziness. Patient denied history of chest pain and convulsions.

On admission, she was in moderate distress, with some shortness of breath, moderate perspiration, and restlessness. The blood pressure was 170/98 mm Hg, with a radial pulse rate of 48/minute and an apical rate of 96/minute. The neck veins were distended; the lungs were clear. The cardiac apex was not felt, but a grade ii systolic ejection murmur was heard along the left sternal border. The pulmonic second sound was greater than the aortic second sound. The remainder of her physical findings were not contributory.

Hemoglobin blood level was 12.4 gm per 100 ml; normal total leukocyte count; trace albumin in the urine, with 30+ red blood cells per high power field. The blood urea nitrogen was 29 mg per cent; serum creatinine 3.2 mg per cent; $CO_2$ combining power 31 mEq/L; serum chloride 89 mEq/L; serum sodium 141 mEq/L; and serum potassium 3.0 mEq/L. The serum uric acid was 10.0 mg per cent.

The electrocardiogram revealed a nodal rhythm and ventricular bigeminy; 250 mg diphenylhydantoin was diluted in 5 per cent dextrose in water and given intravenously over a five-minute period. The appearance of the sinus rhythm occurred concomittantly with the subsidence of the ventricular premature beats. The reversion to sinus rhythm was accomplished by marked symptomatic relief. Diphenylhydantoin was continued orally, 100 mg every six hours, for a total period of four days. Meanwhile, potassium replacement therapy was being undertaken. On the second day of hospitalization ([redacted] 1966), nausea and vomiting had subsided; the rhythm continued to be sinus, while the serum $K^+$ level was still 3.1 mEq/L, despite potassium replacement.

Case 6 - [redacted]: A 47 year old man was admitted to medical service on [redacted]/67 with history of severe substernal pain of 10 days duration, radiating to the left shoulder, arm, and neck, which became worse in the last 24 - 48 hours. During this period, he developed increased SOB, and peripheral edema. In 1960, he was

hospitalized with acute myocardial infarction. For the past several years, he has had angina pectoris, intermittent claudication and night cramps in legs.

On admission, his BP was 140/100, pulse 140 and regular. The pupils were constricted, skin was clammy, and neck veins were distended (VP = 22 cm). Moist rales were present over both lung bases. The heart was enlarged; no murmurs were heard, but a prominent ventricular gallop was present. The liver edge was 2 fingers-breadth below RCM, and pitting edema of the legs was noted.

Hemoglobin 14.2 gms per 100 ml; hematocrit 42.5%; normal total and differential white cell counts; sed. rate 78 mm per hour; BUN 18 mg%; FBS 124 mg%; SGOT 80 units per ml. The electrocardiogram revealed old inferior and recent anterior myocardial infarctions.

The patient was anticoagulated and subsequently placed on Coumadin. He was digitalized and maintained on Digoxin 0.25 mg daily. His condition improved remarkably; his VP became 7 cm and CT 17 sec.

On [redacted]/67, the chest pain recurred and was accompanied with drop in BP (90/60), clammy skin, sinus tachycardia (120/min). He was started on Aramine. On [redacted]/67, he vomited coffee-ground material with 4+ guiac. On [redacted], his condition became stable.

On [redacted], he developed frequent, malignant PVC's, became disoriented. He was started then on Dilantin (100 mg I.V.), and maintained on 300 mg daily. His physical and mental state improved remarkably well, and on [redacted]/67 he started tolerating some physical activities. In the afternoon of [redacted]/67, the interns noticed AV dissociation of the interference type.

Dilantin blood level was 7.78%. Atropine (0.60 mg) subcutaneously reverted this arrhythmia to sinus rhythm (suggesting a vagal stimulation). The arrhythmia recurred and a 2nd dose of Atropine reverted it back to sinus rhythm. Prothrombin time ranged from 33 to 46 sec (control 12 sec). Both Digitalis and Dilantin were discontinued ([redacted]). Digitalis was reinstated on [redacted]/67, and he was discharged home on [redacted]/67. When last seen on [redacted]/68, he was active and doing well.

Table #1

HEMODYNAMIC ACTION OF DILANTIN

| | ACUTE* | DELAYED |
|---|---|---|
| Heart Rate | None | Slows (direct effect on SA node) |
| Cardiac Output | None or Slight | Decrease |
| peripheral Resistance | Decreased | Returned to Baseline |
| Coronary Blood Flow | Increased | Increased (± proportional to dose) |
| Coronary Vascular Resistance | Decreased | Decreased |
| Myocardial $O_2$ Consumption | No Change | No Change |
| Myocardial Contractility | | |
| a) Atrial | Slight Increase | --- |
| b) Ventricular | Slight Decrease | Normal |
| Central Blood Volume | --- | Increased (±) |
| Splanchnic Blood Volume | --- | Increased |

*including the solvent

Table #2

ELECTROPHYSIOLOGIC EFFECTS OF DILANTIN ON CARDIAC MUSCLE

| | DILANTIN | QUINIDINE* | PRONESTYL* |
|---|---|---|---|
| Sinus rate | NSC (28)<br>Increased (38) | Depressed | Depressed |
| Conduction velocity | | | |
| A.V.C.** | Increased (25,26,28,30, 33,39) | Depressed | Depressed (29,39) |
| I.V.C. | Sl. enhanced (38)<br>NSC (25,26,36) | Depressed | Depressed (29,39) |
| Ventricular automaticity | Decreased (25, 26,30,38,39) | Decreased | Decreased |
| Complete Heart Block (experimental) | Unchanged (38) | | |
| Refractory periods (strength-interval curve) | | | |
| a) Atrium | NSC (36,37,38) | Decreased | Decreased |
| b) Ventricle, normal | Decreased (35,36)<br>NSC (37,38) | Decreased | Decreased |
| infarcted | Increased (37) | | |
| Diastolic Threshold | | | |
| Ventricular, Normal | NSC (35,36) | | |
| Infarcted | Increased (37) | | |

* Goodman-Gilman, Macmillan Co., 1965, p. 702.

**Direct effect on AV node.

Table #3

SUMMARY OF THE ANTI-ARRHYTHMIC EFFECTS OF DILANTIN - ITS POTENTIAL USE IN CARDIAC ARRHYTHMIAS

| | | Response |
|---|---|---|
| **Atrial arrhythmias:** | | |
| Premature atrial contractions | | |
| Atrial fibrillation - | induced by Digitalis | Good |
| | not related to Digitalis | Poor (0 - 4%) |
| Atrial flutter | | Poor |
| PAT with block | | Variable |
| Supraventricular tachycardia (nodal) | | Fair (17%) |
| Long-term prophylaxis | | Good (77%) |
| **Ventricular arrhythmias:** | | |
| Tachycardia | a) Digitalis toxicity | Excellent (90%) |
| | b) Myocardial infarction | Good |
| | Prophylaxis | Good (70%) |
| | c) Others - anoxic | Good |
| | P.M.D. | Fair |
| | hypothermia | Poor |
| Multifocal PVC's - depends on cause. | | |

**Side Effects:**

a) With the I.V. use and in patients with left heart failure:

Sinus bradycardia, hypotensions, slow idioventricular rhythm
Ventricular fibrillation (71)
Cardiac arrest (69,70)
Congestive heart failure (68)

b) DPH toxicity:

Enhancing coumadin effect (73)

c) DPH hypersensitivity:

Necrotizing vasculitis (67)

Table #4

RECURRENT (PAROXYSMAL) CARDIAC ARRHYTHMIAS*

| TYPES | NUMBER OF PATIENTS | PREVIOUS MEDICATIONS | RESPONSE TO DILANTIN | | |
|---|---|---|---|---|---|
| | | | EXCELLENT | MODERATE | FAILURE |
| Prem. Ventr. Contractions | 37 | Quinidine, Pronestyl | 26 | 7 | 4 |
| Paroxysmal Atrial Tachycardia | 13 | Sedation, Quinidine, Pronestyl, Digitalis | 10 | 2 | 1 |
| Paroxysmal Atrial Fibrillation | 6 | Digitalis, Quinidine | 6 | 0 | 0 |
| Atrial Flutter | 1 | Digitalis | 0 | 0 | 1 |
| Premature Atrial and Nodal Beats | 3 | Sedation, Quinidine Pronestyl | 3 | 0 | 0 |
| TOTALS | 60 | | 45 (75%) | | |

*Bernstein et al - JAMA 191:695, 1965.

Table #5

RECOMMENDED DOSAGE OF DILANTIN IN THE

MANAGEMENT OF CARDIAC ARRHYTHMIAS

Lang et al: Digitalis-Toxicity (in Dogs), recommended for clinical use, 6 mg/Kg IM, followed 40 minutes later by 1 mg/Kg IV every 10 -15 minutes, until arrhythmia converted (or maximum dose of 15 mg/ Kg is reached).

100 mg diluted in 10 ml of 5% D/W, over 5 minutes. Then continued orally.

Conn: 250 mg IV in 5 ml solvent over 1-3 minutes. a) If no response, no further drug is given. b) If arrhythmia recurs another 250 mg (similarly administered) is given.

Dreifus et al: 5-10 mg/Kg IV to be injected over 15 minutes for treatment of supraventricular and ventricular tachycardias.

Present Recommendations:

Therapeutic: IV, 250 mgs diluted in 10 ml of 5% D/W, slow infusion with continuous ECG monitoring. When arrhythmias converted, switch to either P.O. or IM (100 mg 3-4 times a day).

Prophylactic: IM 100 mg and P.O. 100 mg, then P.O. 100 mg (3-4 times a day).

Lang et al - Arch. Int. Med. 116:573, 1965.
Conn - New Eng. J. Med. 272:277, 1965.
Dreifus et al - Med. Clin. No. Amer. 48:371, 1964.

Table #6

TABLE 1—CLINICAL FINDINGS OF PATIENTS WITH DIGITALIS INTOXICATION

| Case | Age | Sex | Etiology of Heart Disease | Symptoms, Clinical Condition | Types of Arrhythmias | Serum Potassium (mEq/L) | Diphenylhydantoin Dose and Route | Response to Diphenyl-hydantoin |
|---|---|---|---|---|---|---|---|---|
| 1 | 62 | M | HCVD, ASHD | N.V. palpitations | Ventricular tachycardia, atrial fibrillation | 4.8—4.3 | 250 mg IV and 100 mg PO for 2 days | Immediate |
| 2 | 51 | F | Uremic, HCVD | Heart failure, anemia | Ventricular tachycardia | 5.9 BUN=105 | 250 mg IV and 100 mg PO every 6 hours for 4 days | Immediate |
| 3 | 69 | M | Uremic, HCVD | Heart failure, anemia | Multifocal PVCs, PACs | 4.9 BUN=51 | 100 mg IV and 100 mg PO every 8 hours | Immediate |
| 4 | 34 | F | HCVD, Obese | Heart failure, palpitations, anemia | Nodal rhythm, ventricular bigeminy | 3.0 | 250 mg IV and 100 mg PO every 6 hours | Immediate |
| 5 | 75 | M | ASHD | Hemorrhagic necrosis of bowels, N.V. | Ventricular tachycardia, multifocal PVCs, atrial fibrillation | 4.0 BUN=42 | 200 mg IV (in 2 equal doses of 100 mg each) | Immediate |
| 6 | 56 | M | Primary myocardial disease, chronic lung disease | Heart failure, N.V. | Multifocal PVCs, short runs of ventricular tachycardia | 4.1 | 100 mg IV and 100 mg PO every 8 hours | Immediate |
| 7 | 29 | F | RHD, MI | N.V. | Ventricular bigeminy, atrial fibrillation | 2.7 | 200 mg IV and 100 mg every 6 hours | Immediate |
| 8 | 80 | F | Diabetes, ASHD, Hypertension | N.V., chest pain, heart failure | Ventricular bigeminy, ventricular tachycardia, atrial fibrillation | 3.7 | 200 mg IV and 100 mg PO every 8 hours | Immediate |
| 9 | 56 | F | ASHC, HCVD | Heart failure, pneumonia | Atrial fibrillation, multifocal PVCs | 3.4—4.0 | 100 mg IM and 100 mg PO every 8 hours | Within few hours |
| 10 | 79 | F | ASHD | Heart failure | Multifocal PVCs | 2.6 | 250 mg IV and 100 mg PO every 8 hours | Immediate |
| 11 | 69 | M | ASHD, aortic valve disease, uremia | Heart failure | Multifocal PVCs, 1° AV block | 4.5 BUN=115 | 200 mg PO IV and 100 mg PO every 8 hours | |
| 12 | 48 | M | Diabetes mellitus, ASHD, HCVD | Acute MI | PAT with block | 4.1 | Prophylactic therapy | |

HCVD, hypertensive cardiovascular disease; ASHD, arteriosclerotic heart disease; RHD, MI, rheumatic heart disease with mitral insufficiency; N.V., nausea and vomiting; PVCs, premature ventricular contractions; PACs, premature atrial contractions; BUN, blood urea nitrogen in mg per cent.

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