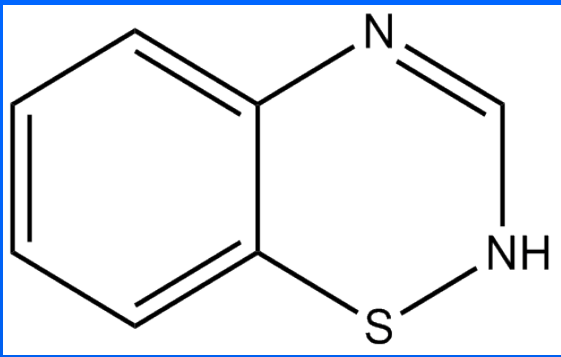


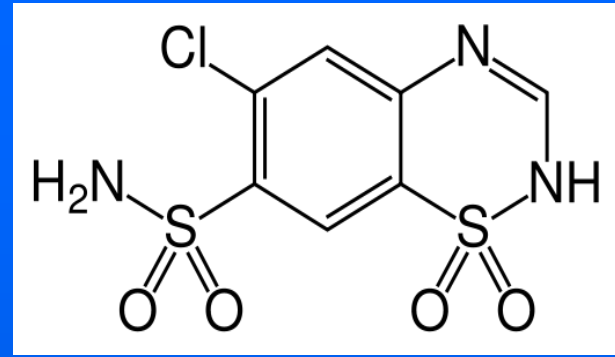


Will Alteration of Radiostrontium Biodistribution by Chlorthalidone Improve Therapy of Painful Bone Metastases?

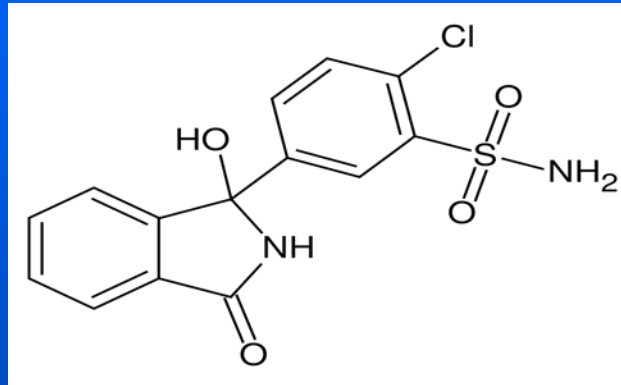
**John J. Coupal
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Benzothiadiazine
Parent of Class



Chlorothiazide
A Thiazide Diuretic



Chlorthalidone
A “Thiazide-Like” Diuretic

Characteristics of Thiazide Diuretics

1. Often 1st-choice drugs for uncomplicated hypertension
2. Increase renal calcium reabsorption occurring secondarily to inhibition of thiazide-sensitive Na^+ - Cl^- co-transporter (NCC)
3. Increase bone mineral density and reduce fractures

DECORPORATION AGENTS

DIURETICS STUDIED INDIVIDUALLY

MECHANISM OF DIURETIC ACTION, OR STRUCTURE

CHLORTHALIDONE	“THIAZIDE-LIKE” (SULFONAMIDE)
DICHLORPHENAMIDE	CARBONIC ANHYDRASE INHIBITOR
METHAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
ACETAZOLAMIDE	CARBONIC ANHYDRASE INHIBITOR
CHLOROTHIAZIDE	THIAZIDE (SULFONAMIDE)
ETHACRYNIC ACID	LOOP DIURETIC (NON-SULFONAMIDE)
AMISOMETRADINE	AMINOURACIL (NON-SULFONAMIDE)

Initial Studies

1. Young-adult virgin female Sprague-Dawley rats injected IP with 0.1 μCi (3.7 kBq) aqueous $^{85}\text{SrCl}_2$.
2. Each intact live animal then counted in large scintillation well (whole-body counter) on either day 2 or day 7 following the $^{85}\text{SrCl}_2$ injection. That initial count deemed 100% Sr-85 retention.
3. Experimental decorporation agent was then given IP to each animal twice daily for up to 3 weeks following initial whole-body count.

• Initial Studies

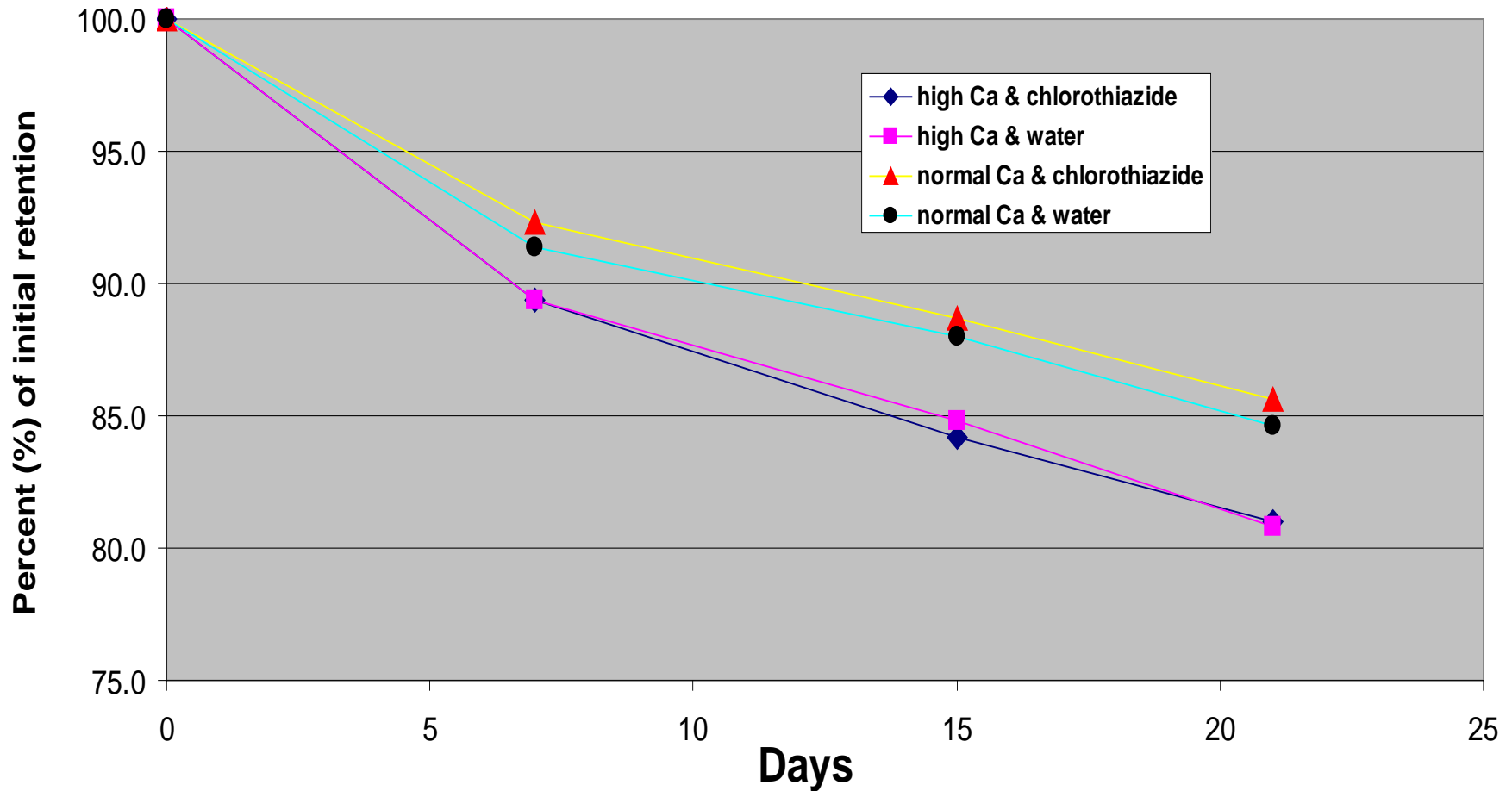
4. During attempted decorporation, all animals consumed either a normal-calcium diet or a high-calcium and tap water *ad libitum*

Normal calcium diet (NCD) nutritionally complete for rat 1.2% Ca and 0.99% P Ca: P ratio 1.21 Vitamin D concentration 4.41 USP U/g

High calcium diet was NCD supplemented with calcium carbonate to yield 3.83% Ca and 0.92 % P; Ca:P ratio 4.16

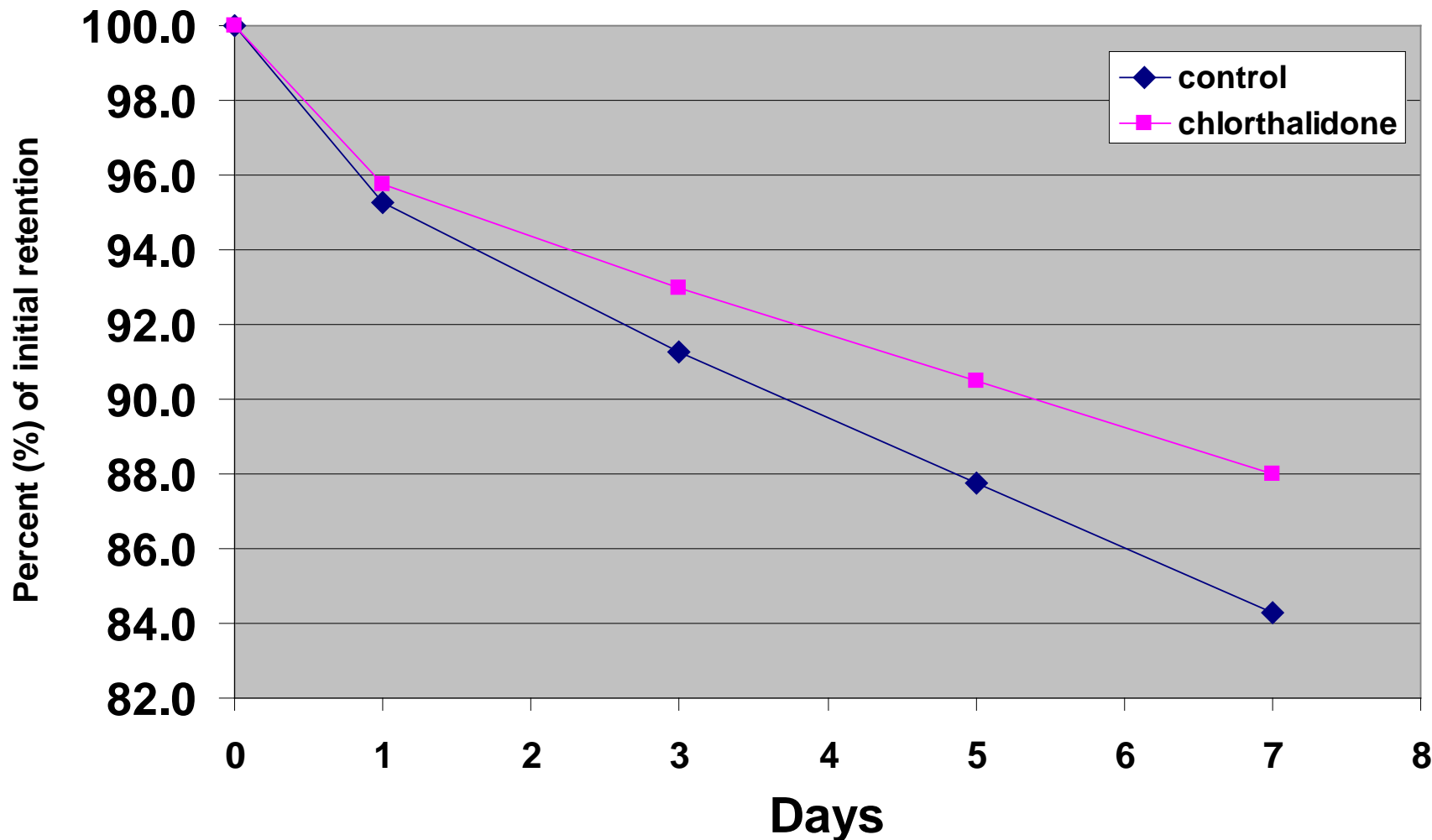
5. Repeated whole-body count on intact animals periodically during decorporation trial.
6. Statistically compared ^{85}Sr whole-body retention of animals getting decorporation agent with that of controls.

Whole-Body Retention of ^{85}Sr



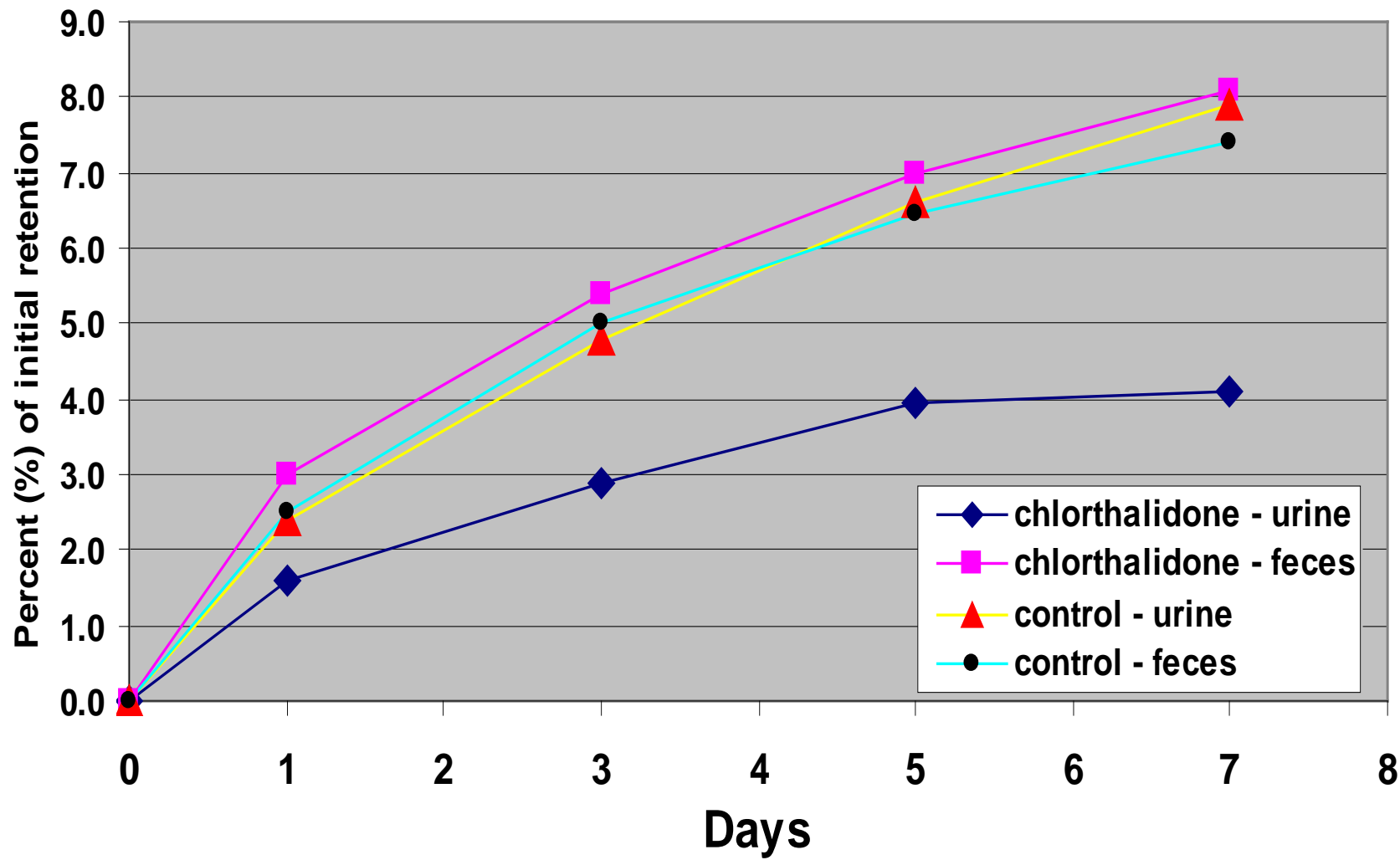
Whole-Body retention of ^{85}Sr by rats consuming either normal or high calcium diet.
Data corrected for radioactive decay.

Whole-Body Retention of ^{85}Sr



Whole-Body retention of ^{85}Sr by rats treated with chlorthalidone.
Data corrected for radioactive decay.

Renal and Fecal Excretion of ^{85}Sr



Cumulative excretion of ^{85}Sr by rats treated with chlorthalidone.
Data corrected for radioactive decay.

Percent of Initial Whole-Body Retention of ⁸⁵Sr on Day 7 of Treatment Period

	<u>chlorthalidone</u>		<u>control</u>		<u>statistical significance</u>
whole-body	88.0	2.0% ^a	84.3	0.8%	P<0.05
total urine	4.6	0.8	7.9	0.8	P<0.001
total feces	8.2	1.3	7.4	0.9	N.S.

^a Mean S.D.

PROPOSED CLINICAL ALTERATION OF ⁸⁹Sr BIODISTRIBUTION

PATIENT INCLUSION: 20 ADULT FEMALES WITH BREAST CANCER &
SKELETAL METASTASES
20 ADULT MALES WITH PROSTATE CANCER &
SKELETAL METASTASES

**Tc-99m OXIDRONATE (Tc-99m HMDP) WHOLE-BODY BONE SCAN
WITHIN ONE WEEK PRIOR TO ⁸⁹SrCl₂ INJECTION**

STUDY DRUG : DOUBLE BLIND RANDOM ASSIGNMENT OF PATIENTS
WITHIN EACH SEX TO RECEIVE EITHER 25MG
CHLORTHALIDONE P.O. , OR ITS PLACEBO

STUDY DRUG REGIMEN: STUDY DRUG STARTED 3 DAYS BEFORE
The 148MBq ⁸⁹SrCl₂ INJECTION, ON THE
DAY OF ⁸⁹Sr INJECTION, AND FOR
14 DAYS THEREAFTER

CLINICAL EVALUATION CRITERIA:

1. PAIN LEVEL DIARY
2. PAIN MEDICATION DIARY
3. PHYSICAL EXAMINATION
4. A) 24-HOUR URINE SAMPLES BEGINNING 3 DAYS PRIOR TO ^{89}Sr INJECTION AND CONTINUING FOR 14 DAYS THEREAFTER:
ASSAY EACH URINE : URINE VOLUME
BONE BIOMAKERS
URINARY CALCIUM
URINARY PHOSPHATE
 ^{89}Sr RADIOACTIVITY
- B) BLOOD: WHOLE BLOOD SAMPLES TAKEN 3 DAYS PRIOR TO INJECTION, 1 DAY AFTER INJECTION, AND AT WEEKLY INTERVALS THEREAFTER FOR 3 WEEKS AT TIME OF BREMSSTRAHLUNG IMAGING

**ASSAY BLOOD FOR: BONE BIOMARKERS
SERUM CALCIUM
SERUM PHOSPHATE
ALKALINE PHOSPHATASE
PROSTATIC ACID PHOSPHATASE
⁸⁹Sr RADIOACTIVITY**

5. BREMSSTRAHLUNG RADIOACTIVITY IMAGING OF PATIENT AXIAL SKELETON AT DAY ONE FOLLOWING ⁸⁹Sr INJECTION, AND THEN WEEKLY THEREAFTER FOR THREE WEEKS.

a. COMPUTE QUANTITATIVE RETENTION OVER 3-WEEK PERIOD

- PATIENT EXCLUSION:**
- 1. PATIENT FROM WHOM QUANTITATIVE URINE COLLECTIONS MAY NOT BE POSSIBLE (e.g., CATHETERIZED PROSTATE CANCER PATIENTS)**
 - 2. PREGNANT FEMALES**
 - 3. HYPERSENSITIVITY TO SULFA DRUGS**
 - 4. CO-EXISTING SEVERE RENAL OR HEPATIC DISEASE**

SPEAKER'S FINAL QUESTIONS

- *WERE BEST THIAZIDES CHOSEN?*
- *WERE BEST DOSES CHOSEN?*
- *DO DIURETICS AFFECT SKELETON, TOO?*
- *DOES ALTERATION OF RADIONUCLIDE BIODISTRIBUTION HAVE A FUTURE?*