MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

May 14, 1964

DIURETICS

CASE # [redacted] [redacted] 43 c/Fe.

Onset of symptomatic hyperthyroidism in [redacted] 1964. Progressively increasing dyspnea, orthopnea and edema began two weeks before admission. Physical examination revealed: BP 110/80, irregular pulse of 140 (auricular fibrillation on EKG), tachypnea, venous distention, rales, cardiomegaly, anasarca and ascites. Thyroid was enlarged and RAI was 89% in 24 hrs.

Treatment:

[redacted] 1964 - Started on digoxin, reserpine, guanethidine and 90 mEq KCl daily. Given 2 cc mercuhydrin.

[redacted] - There had been no response to Rx

initial wt 77.5 Kg ——> 78.5 Kg
pulse 140 ——> 120
initial serum K^+ 3.2 ——> 5.7 mEq/L

[redacted]/64 3:00 p.m. 150 mg Furosemide p.o.
within 1 hour urine flow increased from approximately 30 ml/hr to 800 ml/hr.

10:00 p.m. 100 mg Furosemide p.o.

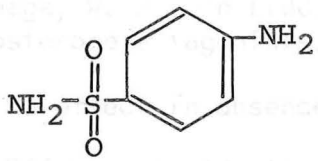
[redacted]/64 8000 ml urine in 18 hrs.; wt. 70.5 kg
Furosemide d.c. Started on Naqua 8 mg/day

[redacted]/64 wt 66.5 kg

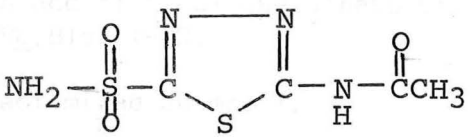
[redacted]/64 wt 62.5 kg Serum K^+ 4.6 mEq/L

[redacted]/64 wt. 61.5 kg

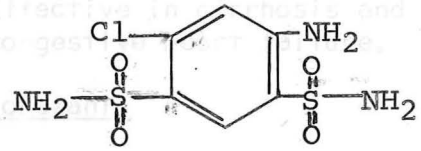
STRUCTURAL RELATIONSHIPS BETWEEN SULFONAMIDE DIURETICS



Sulfanilamide



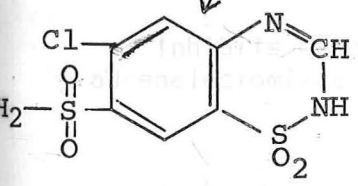
Acetazolamide



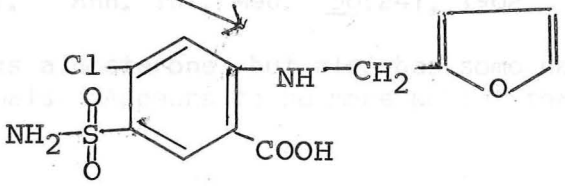
Dichlorphenamide

$NaHCO_3$ Diuresis ↑

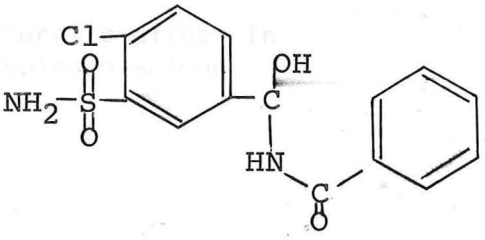
NaCl Diuresis ↓



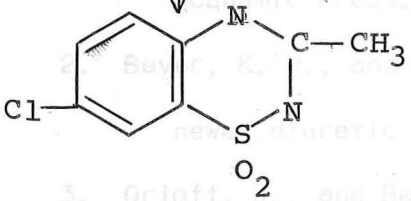
Chlorthiazide



Fursemide

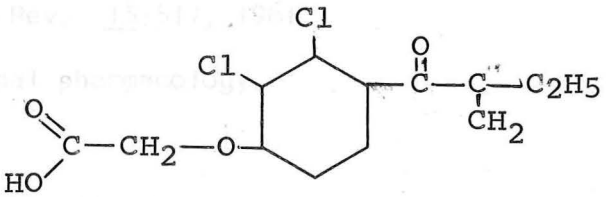


Chlorthalidone



Diazoxide

(non-diuretic hypotensive agent)



Ethacrynic Acid

ALDOSTERONE ANTAGONISTS

A. Criteria

Coppage, W. S. and Liddle, G. W. Mode of action and clinical usefulness of aldosterone antagonists. Ann. N. Y. Acad. Sci. 88:815, 1960.

1. No effect in absence of aldosterone (adrenalectomized animals).
2. Effects of aldosterone will be reversed. Most effective clinically when aldosterone is elevated. Corrects the hypokalemic alkalosis of aldosteronism.
3. Does not inhibit the synthesis or secretion of aldosterone.

B. Spironolactone

Effective in cirrhosis and nephrosis and nephrosis, but much less effective in congestive heart failure.

C. Chlorazanil

Inhibits effect of exogenous aldosterone and DOCA, but also induces natriuresis in adrenalectomized animals. Much less potent than spironolactone.

D. Triamterene

Crosley, A. P., et al. Ann. Int. Med. 56:241, 1962.

Inhibits exogenous aldosterone, but also has some natriuretic effect in adrenalectomized animals. Appears to be more potent than spironolactone.

GENERAL REFERENCES

1. de Stevens, G. Diuretics: Chemistry and Pharmacology. Academic Press. 1963.
2. Beyer, K. H., and Baer, J. E. Physiologic basis for the action of newer diuretic agents. Pharmacol. Rev. 13:517, 1961.
3. Orloff, J., and Berliner, R. W. Renal pharmacology. Ann. Rev. Pharmacol. 1:287, 1961.
4. Pitts, R. F. Physiologic Basis of Diuretic Therapy. Charles C. Thomas. 1959.

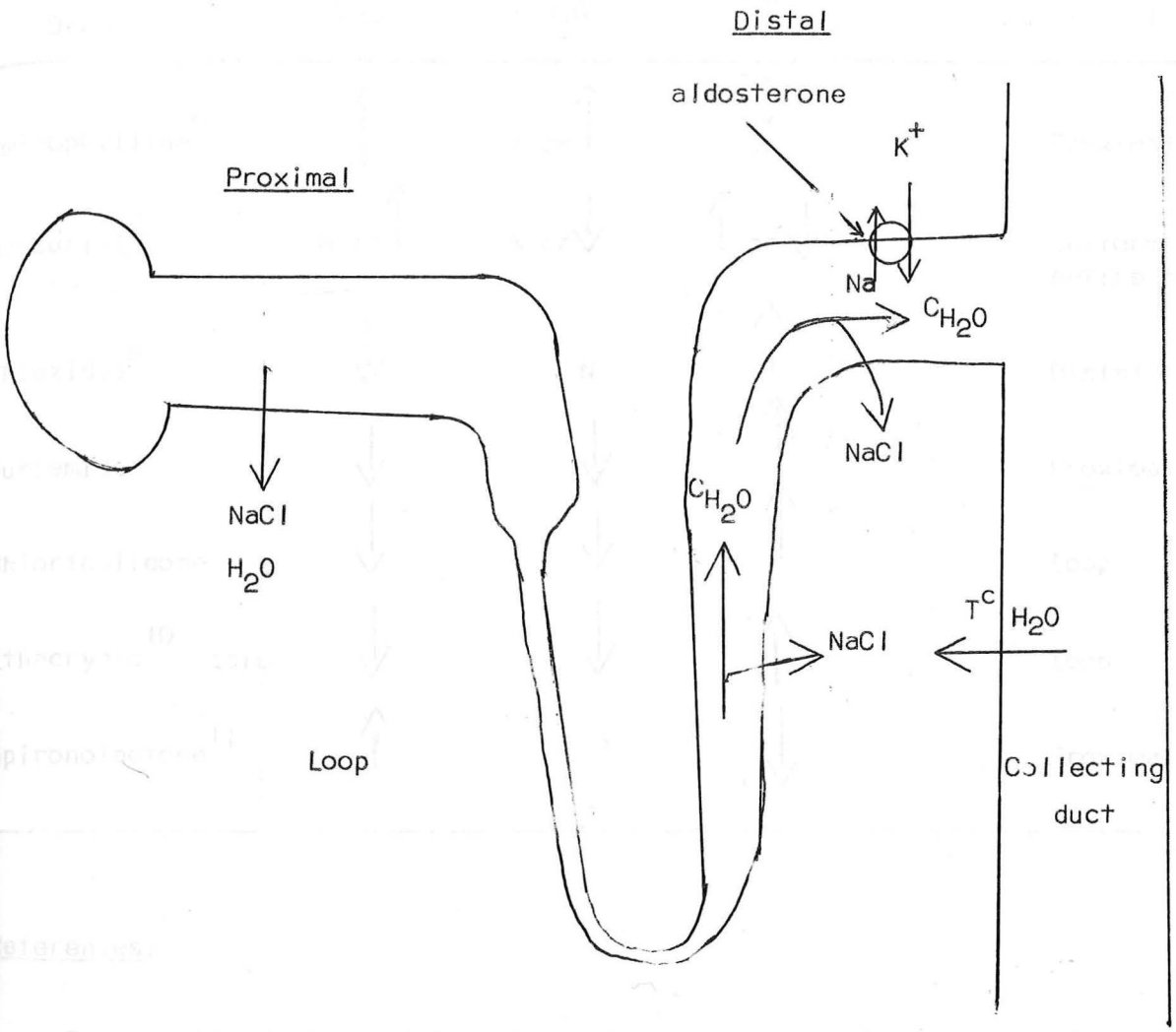
COMPARISON OF RELATIVE DIURETIC POTENCY

Drug	Dosage for max. effect mg/day	Max. Natriuresis % of filt. Na^+ excreted	Kaluresis
Mercurial	2 cc	20%	±
Thiazides			
Chlorothiazide	2000	10%	+ +
Flumethiazide	2000	10%	+ +
Benzthiazide	200	10%	+ +
Hydrochlorothiazide	150	10%	+ +
Benzhydroflumethiazide	20	10%	+ +
Trichloromethiazide	20	10%	+ +
Methylchlorothiazide	10	10%	+ +
Polythiazide	5	10%	+ +
Cyclothiazide	2	10%	+ +
Chlorthalidone	200	10%	+ +
Furosemide[5]	200	35%	+ +
Ethacrynic[6,7] acid	200	15-20%	+ +
Spironolactone	1200	1-2%	-
Triamterene	150	1-2%	-

References:

5. Timmerman, R. J., et al. Curr. Ther. Res. 6:88, 1964.
6. Daley, D., and Evans, B. Diuretic action of Ethacrynic acid in congestive heart failure. Brit. Med. J. Nov. 9, 1963, p. 1169.
7. Melvin, et al. Ethacrynic acid: A new oral diuretic. Brit. Med. J. June 8, 1963, p. 1521.

SITE OF ACTION OF DIURETICS IN THE NEPHRON



Segment	% Na Reabsorbed	C_{H_2O}	$T^C{}_{H_2O}$	K^+ Secretion
Proximal	70-80	-	-	-
Loop	15	+	+	-
Distal	5	+	-	+
Collecting Duct	1-2	-	-	+

Drug	C_{H_2O}	$T^C_{H_2O}$	K^+	Site of Action
Aminophylline[8]	↑	? or ↑	↑	Proximal
Mercurial[8]	N or ↑	N or ↓	↑ or ↓	Uniform along entire tubule
Thiazides[9]	↓	N	↑	Distal
Fursemide	↓	↓	↑	Proximal + Loop
Chlorthalidone	↓	↓	↑	Loop
Ethacrynic acid[10]	↓	↓	↑	Loop
Spironolactone[11]	↑	?	↓	Proximal + Distal

References:

8. Levitt, M. F., and Goldstein, M. H. Mercurial diuretics. Bull N. Y. Acad. Med. 38:249, 1962.

9. Early, E., Kahn, M., and Orloff. Effects of chlorothiazide on urinary dilution and concentration. J. Clin. Invest. 40:857, 1961.

10. Goldberg, M., et al. Effects of Ethacrynic acid on renal diluting and concentrating mechanisms. J. Clin. Invest. 43:201, 1964.

11. Rivera, A., et al. Studies on the localization of aldosterone action on the renal tubule. Steroids 1:91, 1963.

FACTORS INFLUENCING DISTAL SECRETION OF K^+

1. Quantity of Na^+ available at exchange site.

2. Activity of Na^+-K^+-exchange mechanism.

   a. stimulation - aldosterone

   b. inhibitors - spironolactones

      chlorazanil

   c. decreased in renal disease

Conditions where diuretics likely to produce severe K^+ depletion (severe secondary aldosteronism):

1. Cirrhosis with ascites.
2. Long standing congestive heart failure - still partially responsive to diuretics.
3. Malignant hypertension.

Conditions where diuretics + supplemental K^+ may produce severe hyperkalemia:

1. Renal insufficiency (GFR < 30 to 40 ml/min).
2. Severe congestive heart failure which is unresponsive to diuretics.
3. Presence of spironolactone.

References:

12. Edmonds, C. J., and Wilson, G. M. The action of hydroflumethiazide in relation to adrenal steroids and potassium loss. Lancet, March 5, 1963, p. 505.

13. Edmonds, C. J. An aldosterone antagonist and diuretics in the treatment of chronic edema and ascites. Lancet, March 5, 1963, p. 509.

Causes of Refractoriness:

1. Deterioration of primary disease.

   a. decrease cardiac output - ↓ GFR and virtually complete reabsorption of Na^+ in proximal tubule - tendency to develop hyponatremia, hyperkalemia and acidosis.

   b. hepatic decompensation

   c. renal insufficiency (see ref. 14 and 15 below) - Thiazide and mercurial diuretics continue to exert some effect until GFR falls below 15 ml/min. Ethacrynic acid may have an effect with GFR as low as 6 ml/min.

2. Metabolic alkalosis - affects mercurial diuretics only. The non-mercurial diuretics are not influenced by acid-base disturbances.

3. Hyponatremia - Thiazide and mercurial diuretics become less effective when serum Na falls below 130 mEq/L. Ethacrynic acid is completely effective at Na concentrations as low as 120 mEq/L.

4. Hypoalbuminemia - Thiazide and mercurial diuretics are ineffective when serum albumin is less than 1.5 gm%. Ethacrynic acid is effective at serum albumin of 1 gm% or less.

References:

14. Reubi, F. C., and Cottier, P. T. Effects of reduced glomerular filtration rate on responsiveness to chlorthiazide and mercurial diuretics. Circ. 23:200, 1961.

15. Maher, J. F. The use of ethacrynic acid in therapy of edema due to renal disease. Fifteenth Annual Conference on the Kidney. In press.

Side Effects:

A. Secondary to diuretic action.

   1. K-deficiency
      metabolic alkalosis
      muscle weakness & paralysis
      digitalis intoxication
      hepatic encephalopathy

   2. Hyponatremia

   3. Hypovolemic shock

B. Hyperuricemia - all diuretics block the secretion of uric acid in small doses and increase its excretion in large doses. The hyperuricemia can be corrected with probenecid, but probenecid blocks the diuretic action of the thiazides.

Reference:

16. Bryant, et al. Hyperuricemia induced by administration of chlorthalidone and other sulfonamide diuretics. Am. J. Med. 33:408.

Side Effects (Cont'd)

C. Carbohydrate intolerance -
In part due to potassium depletion. However, diazoxide, which has no diuretic activity, has similar effect - appears to block release of insulin.

Reference:

17. Dollery, C. T. Drug induced diabetes. Lancet, Oct. 13, 1962. p. 735.

D. Miscellaneous -

1. Purpura, with and without thrombocytopenia
2. Pancreatitis
3. Dermatitis
4. Photosensitivity
5. Jaundice

Reference:

18. Ford, R. V. Current Concepts in Therapy. Limitations in the use of thiazide diuretics. N. Eng. J. Med. 263:296, 1960 and 263:504, 1960.