CHLOROTHIAZIDE FOR TREATMENT IN TOXEMIAS OF PREGNANCY

by

M. D. ADATIA, M.D., F.C.P.S. F.I.C.S., D.G.O.,

Bombay.

Chlorothiazide is now becoming a very popular and an ideal diuretic. It is an extremely potent and orally effective non-mercurial diuretic agent, and was synthesized by Novello & Sprague in 1957. Its principal action is substantially different from mercurial and other diuretic agents and is also effective in combination with standard hypotensive drugs for the treatment of hypertension. 'Chlotride', manufactured by Merck, Sharp & Dohme, was tried in cases of toxemia of pregnancy and its effects were studied.

Chemistry and Pharmacology

It is known chemically as 6-chloro-7-sulfamyl-1, 2, 4-benozothiadiazine-1, 1-dioxide, and has been designated by the generic name of 'chlorothiazide'. It belongs to a class of heterocyclic compounds of which the parent compound is benzo-1, 2, 4-thiadiazine.

It is a colourless crystalline compound with a molecular weight of 295.7. It has low solubility in water but is readily soluble in dilute aqueous sodium hydroxide. It is soluble in buffer or urine to the extent of about 50 and 150 mg. per 100 c.c. at pH 4 and 7, respectively.

Its clinical trials have been preceded by extensive studies in laboratory animals, showing that even when taken by mouth, it is uniformly and rapidly absorbed; its action starts within a few hours (Baer et al). It does not develop tolerance even after prolonged administration, and is virtually free from gastrointestinal or other disturbing side effects. It is eliminated rapidly by the kidney. At effective doses the compound does not alter significantly glomerular filtration rate or renal plasma flow. It has also ability to counteract the salt retention of adrenocortical steroids. It has a high therapeutic index, the oral acute lethal dose being 8.5 gm. per kilogram of body weight in mice and more than 10 gm. per Kg. in rats, i.e. hundreds of times in excess of the maximum therapeutic dosage in man.

It is mainly a saluretic agent, markedly increases the excretion of sodium and chloride and also possesses carbonic anhydrase inhibitory action (Ford & Moyer). This effect seems to be specific for the renal tubular mechanism. The compound is not concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase. It does not produce acidosis, or any electrolyte imbalance.

Etio-pathology

The exact cause of toxemia of pregnancy is still not known but one

thing seems to be certain that there is some metabolic defect which leads to abnormal handling of water and electrolytes. Dieckman has demonstrated that elimination of water ingested or injected is delayed in pregnant women and to a greater degree in women with toxemia of pregnancy. Hughes & Venning have observed that sodium retention in toxemic women is due to increased excretion of adrenocortical steroids. In any case factors responsible for excessive sodium retention or increased reabsorption should be responsible in the pathogenesis of toxemia of pregnancy (Chesley).

Increased ingestion of water leads to diuresis but with this excretion of sodium is diminished. Slight edema is easily cleared out by administration of ammonium chloride. But when edema is more it does not bring satisfactory diuresis. Assali has found that toxemic women who have decreased sensitivity to ammonium chloride are unable to mobilize the retained amounts of sodium. Mercurials bring good diuresis in cases of edema with congestive cardiac failure, but are not advisable for cases of nephritis because they might damage the tubular mechanism by their direct toxic action. Recent biopsy studies have shown that the lesion of toxemia resembles nephritis (Dieckman & Potter), and thus it would be inadvisable to use mercurials for toxemic patients.

Acetazolamide gives excellent diuretic effect in edema states of pregnancy but develops resistance by prolonged administration and is unable to control edema in congestive cardiac failure. A synthesis of a non-mercurial compound possessing biological properties of both organic mercurials and carbonic anhydrase inhibitors has brought into existence 'Chlorothiazide'. It has undergone repeated trials and research (Novello & Sprague).

Ford & Spurr have studied and shown that Chlorothiazide is efficient in congestive heart failure and in pregnancy edema. Acetazolomide is reported to have developed drug resistance (Hanley et al) while chlorothiazide maintains effective diuresis even after prolonged administration and is effective in many cases that do not respond to other diuretic agents (Finnerty et al). It is also suggested by observation and study (Finnerty et al) that possibly the action of chlorothiazide is not through inhibition of carbonic anhydrase but possibly by direct action on renal tubular transport mechanism. Trials made by *Freis* et al show that oral administration of chlorothiazide has antihypressive effect and it also potentiates the effects of the hypotensive drugs and thus is a more suitable drug for toxemic cases. It is observed by some workers that the antihypertensive effects of chlorothiazide, apart from the effect of excessive salt depletion, may be due to direct hypotensive action (Hollander and Wilkins). It is also interesting to note that the blood pressure of normotensive is not reduced by this drug.

Another advantage is that potassium level is not disturbed by even prolonged administration of chlorothiazide. Possibly because it is rapidly absorbed and starts its action immediately and gets eliminated very soon by the kidney. The patients get sufficient time to get satisfactory distribution of ingested potassium be-

fore the second dose is given. Thus electrolyte depletion is not likely to take place within the dosages advocated even if it is continued for a long time. Only in exceptional circumstances when the drug is continued in combination with diets very low in sodium or when external loss is occurring due to protracted vomiting, diarrhoea or fever, that it might lead to severe electrolyte imbalance when potassium administration might be required. But further experience and time is necessary to determine the effectiveness of the drug in such conditions.

Clinical Material and Results

40 cases of pre-eclampsia were tried with 'Chlotride' and are compared with a control series of 40 other cases. The patients were clinically examined and their blood pressure, record of weight and complete urine analysis were done. They were checked up at weekly interval. Out of them, 10 patients were kept indoors for an additional therapy of a hypotensive drug. These patients had history of previous hypertension or their blood pressure was more than 150 systolic. Serpasil tablets of 0.25 mgms. were given twice a day to them.

Doses and Duration

All patients in trial series were given one tablet of 'chlotride' 500 mgms. twice a day. The treatment was continued for two weeks to ten weeks, depending upon the clinical response. In the control series calcium tablets were given in exactly similar way.

Results

The weight loss was found to be varying from about 0 lb. to 18 lbs. per week. The complete clearance of edema was seen in 29 patients, only decrease of edema was seen in 7 patients and 4 patients showed no change in edema. About 20 mm. reduction of systolic blood pressure was seen in 80% of the cases. The decrease in the amount of albuminuria was noted as follows:—

4+ to 0 in 6 patients, 3+ to 0 in 11 patients and 2+ to 0 in 23 patients. Their ages varied from 18 to 40 years and parity from I to XI, out of which seven were primiparous. Studies of plasma electrolyte concentrations were not done in the series.

Dosage and Toxicity

The dose administered was 1000 mgms. per day. One tablet of 500 mgms. was given in the morning and the other in the afternoon. The onset of action was occurring in first two hours and the peak of action was in 4 to 6 hours.

The only toxic manifestation noted when chlorothiazide was given to pregnant patients was mild nausea in 3 patients and occasional paresthesia of extremities, malaise and fatigue in 2 patients. But continued administration did not give relief in 4 patients.

In the control series similar cases were selected. They were also clinically examined every week and their blood pressure, weight and urine were also checked up. In every case there was marked increase in weight. The weight gain varied from 8 to 13 lbs. in a week. They were given calcium tablets as placebo. Out of

Chlotride in Cases with Toxaemia and Pregnancy

No.	Name	Age	Para	Weight	Blood pressure	Toxic symptoms	General condition	Baby	Edema	Albuminuria	
1.	I.R.S.	34	vi, 5 FTND.	144, 140, 137, 135	150/100, 140/100, 130/100, 130/90	Nil	Good	Good, 7-14	Cleared	++	Cleared
2.	J.B.C.	30	iv, 1 FTND, 1 LSCS Pl. Previa, 1 Abort.	113, 108, 102	140/80, 140/80, 120/80	Nil	Good	Good, 6-10	Cleared	+++	„
3.	J.S.G.	24	iii, 1 FTND, 1 Premature died	139, 130, 122, 121	160/110, 140/100, 140/100, 130/90	Nil	Good	Good, 7-4	Cleared	++	„
4.	J.A.S.	34	ix, 7 FTND, 1 Abort.	163, 150	150/114, 120/90	Nil	Osteo Malacia	Good, 8-12	Decreased	++	„
5.	J.J.K.	30	vi, 3 FTND, 2 Abort.	186, 174, 168	160/110./ 144/100, 120/80 120/80	Nil	Hospitalized	Good, 6-6	Cleared	+++	„
6.	J.H.J.	35	vii, 5 FTND, 1 Abort.	160, 150, 140	140/100, 130/100, 120/90	Paresthesia & Fatigue	Good	Good, 7	Cleared	+++	„
7.	J.N.J.	31	iv, 2 FTND, 1 Abort.	188, 179	130/80, 120/80	Nil	Good	Good, 6-15	Cleared	++	„
8.	J.K.G.	33	iii, 1 FTND, 1, 8 months stillborn	159, 156, 154, 150, 150	160/110, 150/100, 140/100, 130/80, 120/80	Nausea	Hospitalized	Good, 6	Cleared	++++	„
9.	K.P.S.	21	i	120, 116, 111	130/90, 110/80, 110/70	Nil	Good	Good, 6-12	Decreased	++	
10.	K.S.K.	40	x, 8 FTND, 1 Abort.	127, 128, 128, 129	140/100, 120/80, 130/90, 140/100	Nil	Weak	Twins Breech, 5-11 & 5-3	No change	+++	„
11.	K.B.R.	26	v, 4 FTND	150, 143, 139, 133	170/100, 140/110, 140/100, 115/70	Nil	Hospitalized	Good, 7-8	Cleared	+++	„
12.	K.P.B.	25	iv, 3 FTND	113, 103, 99, 94	140/90, 130/90, 130/90, 130/80	Nil	Good	Good, 6-4	Cleared	++	„
13.	K.S.S.	22	i	129, 124, 121	130/90, 120/80, 110/70	Nil	Good	Good, 6-10	Cleared	++	„
14.	B.S.V.	30	vi, 4 FTND, 1 Premature died	146, 136, 127, 124 123	150/100, 150/90, 130/90, 120/80, 120/80	Nil	Good	Stillborn	Cleared	++	„
15.	H.M.P.	22	i	142, 132, 125	188/135, 165/120, 140/100, Eclampsia	Nil	Weak, Hospitalized	Weak, 4-2	Cleared	+++	„
16.	H.V.K.	20	iii, 1 FTND, 1 Abort.	97, 93, 88, 82	180/100, 130/100, 130/100, 130/100	Nausea	Weak, Hospitalized	Weak, 4-12	Cleared	++++	„
17.	K.K.S.	35	vi, 6 FTND	151, 145, 142	130/90, 120/80, 120/80	Nil	Good	Good, 6-10	Cleared	++	„
18.	K.G.B.	22	iv, 1 FTND, 2 Abo.	109, 109, 110, 110	130/80, 130/80, 140/80, 140/80	Nil	Good	Good, 6-2	No change	++	„

19.	K.B.S.	18	i	[illegible], 124, 116, 109	190/130, 170/130, 140/100, 140/100	Nil	Weak, Hospitalized	Weak, 2-12	Cleared	++++	„
20.	A.D.V.	20	i	147, 137	140/90, 120/80	Nil	Good	Good, 6-6	Decreased	+++	„
21.	A.A.M.	23	ii, 1 FTND	144, 138, 136, 131 131, 126, 122	140/80, 120/80, 110/70, 130/90, 130/90, 120/80	Nil	Weak	Good, 8 lbs.	Cleared	++	Cleared
22.	B.C.S.	25	iii, 2 FTND	115, 110	140/70, 120/80	Nil	Good	Good, 5-3	Cleared	++	„
23.	B.J.S.	29	iv, 3 FTND	130, 127, 123, 120	130/70, 120/80, 100/80, 115/80	Nil	Good	Good, 7-3	Cleared	++	„
24.	B.H.M.	23	iii, 1 FTND 1 LSSC, Pl. Previa	135, 127, 127, 128	140/110, 140/110, 140/90, 120/80	Paresthesia & Fatigue	Good	Good, 6-1	Decreased	+++	„
25.	C.J.P.	32	v, 3 FTND, 1 Abort.	113, 102, 104	150/90, 150/100, 110/80	Nil	Weak	Good, 5-12	Cleared	++	„
26.	D.D.J.	20	ii, 1 Premature, 8 mths., stillborn	107, 98, 96	160/100, 120/80, 120/80	Nil	Hospitalized	Good, 6-2	Cleared	+++	„
27.	D.H.M.	31	v, 4 FTND	111, 106, 104	140/100, 140/100, 120/80	Nil	Good	Good, 5-8	Cleared	++	„
28.	D.K.B.	27	vi, 5 FTND	144, 145, 147, 147	120/80, 140/100, 130/100, 130/110	Nil	Good	Good, 7	No change	++	„
29.	L.D.D.	25	iii, 2 FTND	160, 156, 154	140/90, 140/90, 120/80	Nil	Good	Good, 8-8	Cleared	++	„
30.	L.T.J.	35	viii, 3 FTND 4 Abortions.	134, 128, 127, 121	150/90, 140/90, 140/90, 120/80	Nil	Good	Good, 7-13	Cleared	+++	„
31.	L.M.T.	30	vi, 6 FTND	156, 151, 146	140/90, 130/90, 120/70	Nil	Good	Good, 7-7	Decreased	++	„
32.	L.L.K.	29	viii, 4 FTND, 2 Abortions.	138, 138, 121	140/90, 130/80, 130/90	Nausea	Good	Good, 7-2	Cleared	++	„
33.	L.B.M.	27	iv, 3 FTND	143, 134, 134	140/100, 120/80, 120/80	Nil	Good	Good, 7-2	Cleared	+++	„
34.	L.V.M.	22	ii, 1 FTND	147, 139, 136	150/100, 150/100, 140/90	Nil	Good	Good, 5-4	Cleared	++++	„
35.	L.P.P.	38	viii, 7 FTND	118, 109	170/110, 140/90	Nil	Hospitalized	Good, 5-14	Decreased	++	„
36.	L.C.S.	35	ii, 1 FTND	146, 140, 131	160/100, 150/100, 140/90, 130/90	Nil	Hospitalized	Good, 6-8	Cleared	+++	„
37.	M.K.T.	25	iv, 3 FTND	132, 132, 134, 136	140/80, 140/80, 120/80, 120/90	Nil	Good	Good, 7-10	No change	++	„
38.	M.K.M.	33	viii, 7 FTND	111, 93, 92, 91, 94	230/126, 210/120//180/110, 150/100, 140/90	Nil	Weak, Hospitalized	Stillborn	Cleared	+++	„
39.	M.M.K.	22	i	143, 131, 131	140/100, 130/90, 130/90	Nil	Good	Good, 6-7	Decreased	++	„
40.	M.S.M.	38	xi, 8 FTND, 2 Abortions.	164, 157, 146	150/100, 140/90, 130/90	Nil	Good	Good, 7-2	Cleared	++	„

Control Series

No.	Name	Age	Para	Weight	Blood pressure	Toxic symptoms	General condition	Child	Edema	Albuminuria	
1.	S.P.R.	28	iv, 3 FTND	120, 123, 126, 132, 134, 138	140/90, 146/110, 150/100, 150/100, 160/110	Nil	Good	Good, 6-10	Present	+++	
2.	S.J.S.	29	iii, 2 FTND	154, 164, 169, 173	140/80, 140/80, 140/80, 130/80	Nil	Obesity	Good, 8-8	Present	+++	
3.	S.K.J.	30	xi, 8 FTND, 2 Abortions.	92, 98, 96	130/90, 130/90, 120/90	Nil	Good	Good, 4-15	Decreased	+++	Cleared
4.	S.S.D.	30	i	121, 120, 126, 128	140/80, 120/80, 140/90, 140/70	Nil	Good	Good, 5-5	Present	+++	
5.	S.V.G.	35	iii, 1 FTND, 7 mths. 1 Premature,	118, 118, 122	170/110, 160/100, 160/100	Nil	Good	Good, 6-5	Present	+++	
6.	S.N.B.	30	v, 4 FTND	140, 149, 149, 152, 154	124/80, 170/120, 160/100, 160/110, 180/120	Nil	Good	Good, 5-8	Present	+++	
7.	S.G.P.	28	iii, 2 Abortions.	112, 115, 115, 121	140/90, 160/100, 160/100, 170/100	Nil	?Pl. Previa	Good, 6-9	Present	+++	
8.	S.R.G.	25	vii, 6 FTND, 3 girls, living, 3 boys died.	174, 172, 176, 180, 188, 189	140/100, 120/80, 120/80, 150/100, 180/110, 180/90	Nil	Good	Good, 6-12	Present	+++	
9.	R.A.M.	23	iii, 2 FTND	96, 100, 104, 109, 109	140/90, 120/80, 140/100, 150/110, 140/80	Nil	Good	Good, 6-8	Present	+++	
10.	R.S.G.	25	v, 4 FTND	98. 106, 104	120/80, 130/90, 140/80	Nil	Good	Good, 7-14	Decreased	+++	
11.	R.K.S.	35	v, 1 Premature, 1 FTND, 1 Abort, 1 ectopic.	151, 150, 164	150/100, 130/90, 170/110, 190/120	Nil	Good	Stillborn	Present	+++	
12.	R.S.M.	30	vii, 5 FTND, 1 Abortion	205, 199, 204, 206	140/100, 140/80, 140/80, 140/100	Nil	Weak	Good, 5-2	Increased	+++	
13.	S.S.T.	33	vii, 6 FTND	116, 121, 122	130/80, 140/100, 140/80	Nil	Good	Good, 8-12	Present	+++	
14.	S.R.S.	24	i	112, 114, 117, 121	140/90, 130/90, 130/100, 150/110, 150/100	Nil	Good	Good, 5-7	Present	++++	
15.	S.V.S.	35	vi, 4 FTND, 1 Abortion.	99, 98, 100, 105	158/120, 130/90, 160/110, 220/150	Nil	Post-partum psychosis 2 years back	Stillborn	Increased	+++	
16.	S.K.S.	30	iv, 3 FTND	137, 146, 156, 153	140/90, 130/80, 120/100, 140/100	Nil	Good	Good, 8-9	Present	++	
17.	S.R.B.	24	ii, 1 FTND	123, 125, 128, 129	140/80, 130/80, 140/80, 130/80	Nil	Good	Good, 8-4	Present	++	Cleared

18.	S.V.R.	25	iii, 2 FTND	131, 141, 140, 143	160/100, 150/90, 160/90, 150/90, 150/90	Nil	P.P.H., Blood transfusion	Good, 5-8	Increased	+++	
19.	S.K.J.	33	vi, 5 FTND	102, 103, 105, 105	140/80, 140/90, 140/80, 150/90, 160/100	Nil	Good	Good, 7-10	Present	++	
20.	S.T.V.	19	ii, 1 FTND	108, 111, 112	140/90, 140/70, 140/80	Nil	Good	Good, 6-1	Present	++	Cleared
21.	S.K.S.	19	i	106, 116, 119	140/80, 140/100, 140/100	Nil	Good	Stillborn	Present	+++	
22.	S.C.B.	24	iii, 2 FTND	147, 155, 158	130/80, 130/90, 130/90	Nil	Good	Good, 6-10	Present	++	
23.	V.K.P.	30	vii, 6 FTND	107, 117, 119	120/80, 130/90, 130/90	Nil	Good	Good, 7-6	Present	++	
24.	V.J.P.	24	iv, 3 Abortions	101, 108, 119	130/90, 130/90, 140/100,	Nil	Caesarean Section	Good, 7-4	Present	+++	
25.	V.P.R.	34	vi, 3 FTND, 2 Abortions	137, 140, 144	130/80, 140/90, 140/100	Nil	Good	Good, 6-2	Present	++	
26.	V.B.D.	35	vi, 4 FTND, 1 Premature	107, 117, 109, 112	130/80, 160/100, 150/110, 170/110	Nil	Anaemic	Good, 5-2	Decreased	+++	
27.	U.K.M.	21	ii, 1 Abortion	104, 114, 114, 119	130/90, 130/90, 140/100, 130/90	Nil	Good	Good, 6	Present	+++	
28.	Y.P.M.	25	i	120, 128, 130, 131	130/90, 172/125, 180/120, 160/120	Nil	Breech Delivery	Weak	Present	+++	
29.	T.M.M.	39	vii, 6 FTND	127, 129, 129, 129	130/80, 130/90, 140/100, 140/100	Nil	Good	Good, 6	Decreased	+++	
30.	T.D.B.	35	viii, 6 FTND, 1 Abortion.	140, 142, 143, 143	130/90, 160/110, 130/100, 130/100	Nil	Good	Good, 7-3	Present	++	Cleared
31.	T.B.P.	26	v, 3 FTND, 1 Abortion.	109, 112, 113, 115	125/90, 154/100, 130/90, 160/110	Nil	Treated with Digoxin	Twins, 4-2 & 4-4	Present	+++	
32.	S.B.S.	32	v, 4 FTND	166, 168, 173, 164	130/90, 140/100, 150/105, 150/110	Nil	Good	Good, 6-4	Present	+++	
33.	S.U.G.	38	viii, 5 FTND, 2 Abortions.	128, 136, 139, 140	110/90, 130/90, 130/90, 142/110	Nil	Mid-Cavity Forceps	Stillborn	Present	++++	
34.	R.M.A.	25	iv, 2 FTND, 1 Abortion.	137, 139, 144	146/100, 150/110, 160/110	Nil	Good	Good, 5-2	Present	++	
35.	R.J.C.	21	i	135, 142, 149	120/80, 120/80, 130/90	Nil	Weak	Good, 5-5	Increased	++	
36.	S.K.P.	26	iv, 2 FTND, 1 Abortion.	108, 108, 107, 110	140/100, 130/90, 150/110	Nil	Obstetric Shock	Good, 7-2	Present	+++	
37.	S.V.G.	20	ii, 1 FTND	110, 114, 119, 124	120/80, 130/90, 150/100, 150/100	Nil	Good	Good, 6-12	Present	+++	
38.	S.N.J.	30	vi, 5 FTND	143, 147, 151	140/100, 150/110, 150/110	Nil	Good	Weak, 4-9	Present	+++	
39.	S.J.L.	30	vii, 6 FTND	140, 146, 150	130/80, 150/100, 160/110	Nil	Good	Good, 7	Present	+++	
40.	T.P.B.	28	iv, 3 FTND	114, 124, 125, 128	130/80, 130/90, 130/90, 140/100	Nil	Forceps delivery	Good, 7-4	Present	++	

the 40 cases, edema decreased in 4 cases only by bed rest. Five cases showed increase of edema and rest of them showed persistence of edema. Blood pressure also remained high or increased in many cases. The albuminuria was cleared up in 4 cases and the rest of them did not show any change. Their ages varied from 19 to 38 years and parity from I to XI, out of which 6 were primiparaes. So far as the variation in weight was concerned 2 of them reduced in weight, 3 remained constant and remaining ones increased in weight. The maximum increase of weight was 19 lbs.

Comments

In 30% to 40% of normal pregnant women, edema of varying degrees appears from the fifth or sixth month of gestation without rise of blood pressure or albuminuria, but it subsides with rest in bed, elevation of the foot of the bed and restriction of salt in the diet. These patients under trial were also selected and everyone had definite edema, albuminuria and rise of blood pressure. They were compared with similar cases who were given only bed rest and no medication except calcium tablets.

Initial weight loss in the cases under trial was most marked in the first week. They were all taking usual balanced salt diet. Only excess of salt was omitted. In 4 cases, in whom it was continued for even eight weeks, no reduction of edema was observed, and the tablets were not found to be effective.

Apart from diuretic properties, chlorothiazide also showed definite antihypertensive effect. It had no toxic effects and nobody developed tolerance but 4 cases did not show reduction of edema. The greatest advantage was that it could be given orally in very simple dosage schedule (twice a day, morning and afternoon). No restriction of salt was imposed on the patients and this created a great pleasing effect on them.

Whenever more reduction of blood pressure was necessary a small dosage of serpasil was added which gave very satisfactory results.

Thus chlorothiazide was an ideal diuretic for the treatment of toxemias of pregnancy. If given alone at the first sign of excessive weight gain or slight elevation of blood pressure it would frequently reverse the toxemic process. This property would enable chlorothiazide therapy to be started at the first prenatal visit, for the hypertensive patient who is more prone to develop toxemia. When given in combination with Serpasil in the patient with severe toxemia, chlorothiazide, in addition to exerting its diuretic effect, greatly enhanced the potency of the antihypertensive agent. Four cases, for unexplainable reasons, did not respond to chlotride.

Summary

40 patients with edema, albuminuria and hypertension or toxemia received 'Chlorothiazide' and its results are compared with a control series of equal number. It produced very effective diuresis in most of these patients. The reduction of edema and lowering of blood pressure was very significant compared to the control series. It was found to be potent orally, and an active non-toxic

diuretic. It also enhanced the potency of antihypertensive agents.

The absence of toxic manifestations, excepting the symptoms of mild nausea, occasional paresthesia, malaise and fatigue, make it an ideal drug. Only four cases did not respond to chlorothiazide therapy.

Chlorothiazide is thus observed to be a valuable adjunct to current methods of treating pre-eclampsia patients.

References

1. Assali N. S., Herzig O. and Singh B. P.: J. Appl. Physiol.; 7, 367-374, (Jan.) 1955.
2. Baer J. E., Leidy L. and Brooks A. V.: Fed. Proc.; 16, 278, 1957.
3. Chesley L. C., and Chesley E. R.: Am. J. Obst. & Gyn.; 45, 748 (May) 1943.
4. Dieckman W. J. and others: Am. J. Obst. & Gyn.; 58, 1014, (Nov.) 1949.
5. Dieckman W. J., Potter E. L. and McCartney C. P.: Am. J. Obst. & Gyn.; 73, 1-16, (Jan.) 1957.
6. Finnerty Frank A. (Jr.), Joachim H. Buchholz, and John Tuckmann: Jour. Amer. Med. Asso.; 11, January 1958.
7. Ford R. V. and Spurr C. L.: Am. J. Med.; 22, 965, (June) 1957.
8. Ford R. V., Moyer J. H., Spurr C. L., and Handley C.: M. Rec. & Ann; 51, 376-378, (April) 1957.
9. Freis D. Edward, Wanko Annemarie, Wilson Ilse M., Parrish Alvin E.: J. Amer. Med. Asso.; 11, January 1958.
10. Hanley T., and Platts M. M.: J. Clin. Invest.; 35, 20-30, (Jan.) 1956.
11. Hollander W., and Wilkins R. W.: Boston M. Quart.; 8, 69-75, (Sept.) 1957.
12. Hughes E. C., and others: Am. J. Obst. & Gyn.; 67, 782-800, (April) 1954.
13. Novello F. C., and Sprague J. M.: J. Am. Chem. Society; 79, 2028-2029, (April 20) 1957.
14. Venning E. H., Carballeira A., and Dyrenfurth L.: J. Clin. Endocrinol; 14, 784, (July) 1954.