CENTRAL DIABETES INSIPIDUS AND ITS MANAGEMENT WITH ORAL ANTIDIURETIC AGENTS

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Artinine Vasopressin (AVP) the main antidiuretic hormone is secreted by supraoptic nucleus of the hypothalmus and transported to the posterior pituitary for the purpose of storage and released via hypothalmic hypophysical tract. Vasopressin exerts its main action i.e. conservation of water at distal renal tubule by enhancing the reabsorption of free water. It is postulated that this action is mediated through cyclic AMP system.

With the development of a sensitive radioimmunoassay measurement of vasopressin in blood, we have defined the factors controlling ADH release (ref. 1-3). The OSMO receptors are sensitive to serum osmolality which is mainly due to serum sodium. Rise in serum osmolality due to the infusion of hypertonic saline will increase AVP secretion. Other extra cellular solutes like mannitol and urea also have similar effect. Glucose, being both an extra and intra cellular ion has a paradoxical effect (Fig. 1).

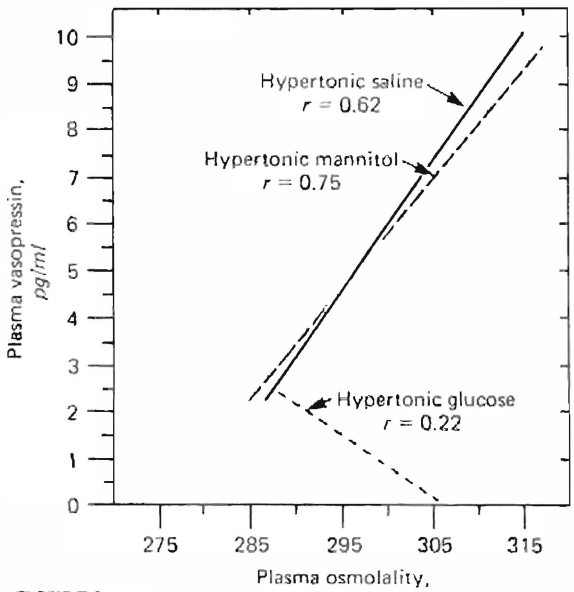

FIGURE 1

AVP secretion is stimulated by Hypovolemia (due to dehydration or hemorrhage), hypotension (postural or drug induced), nicotin and angiotension II. ADH release is inhibited by hypoosmolality due to ECV expansion by water ingestion (29 ml/kg BW). Alcohol and dilantin also have been reported to have a central inhibiting effect. Drugs like lithium and chlortetryacycline do not have effect on ADH release but poison adenyl cyclase in the distal renal tubule which is needed for the action of ADH through cyclic AMP system.

When a patient with symptoms of excessive thirst presents, the cause of polydipsia due to polyuria could be in the hypothalmic-pituitary damage (central diabetes insipidus) or reduced ADH response to renal tubules (nephrogenic DIL). Osmodiuresis (diabetes mellitus) or psychogenic (compulsive water drinking). Pathophysiology and differential diagnosis of three forms of polyuria are shown in Fig. 2 and 3.

The central diabetes insipidus is also of 4 types depending on the severity of the lesion leading to complete DI (Type 1) to partial (Type 2, 3) and near normal or subnormal urine concentration (Type 4). Clinical clues in history especially that of head injury and granolomatous infection are helpful. Nearly 60% of central DI is now as result of either surgery or injury in the hypothalmic-pituitary area, 30% due idiopathic reasons and 10% due to various CNS infections. Patients with psychogenic polydipsia usually do not have abrupt onset of DI, nor do they have nocturnal polyuria.

A reasonable workup for polyurea-polydipsia syndrome should include careful daily intake output record for several days, serum electrolytes, blood glucose, urine specific gravity, serum and plasma osmolality at the same time and fluid restriction test. Hypertonic saline infusion and response to pitressin test should be done carefully and under close supervision. Depending upon above test and clinical history, and anterior pituitary investigation, sella x-rays with tomogram and CT. scan of pituitary with air contrast is suggested. On the other hand if the diagnosis leads toward nephrogenic DI then careful evaluation of renal function and detail drug history is advised. For compulsive water drinking psychological evaluation may be helpful.

Patients with central DI are unable to concentrate their urine depending on the amount of ADH available. Therefore their urine osmolality will be low for a given plasma osmolality and plasma AVP (ADH) will be low (see Fig. 4-5). On the other hand

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PATHOPHSIOLOGY OF POLYURIA

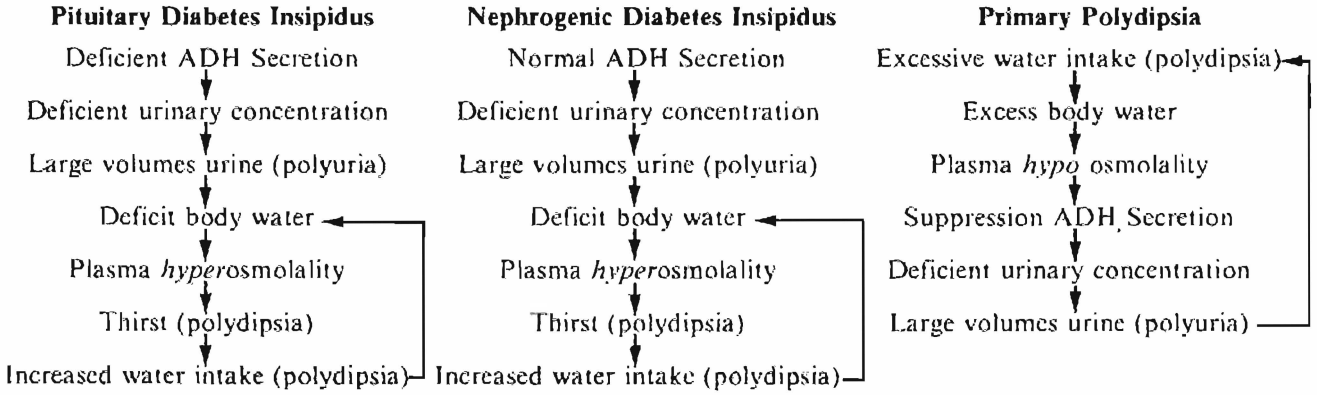


FIGURE 2

POLYURIA-DIFFERENTIAL DIAGNOSIS

	Plasma Osmolality	Urine Osmolality		
	Basal	**Basal**	**Dehydration**	**Pitressin**
Normal	282-294*	600-1100*	900-1300*	600-900*
Diabetes Insipidus Pituitary	Normal or *High*	Low	Low	Normal
Diabetes Insipidus Nephrogenic	Normal or *HIgh*	Low	Low	Low
Primary Polydipsia	Normal or *Low*	Low	Low-Normal	Low-Normal

*mOsm/Kg

FIGURE 3

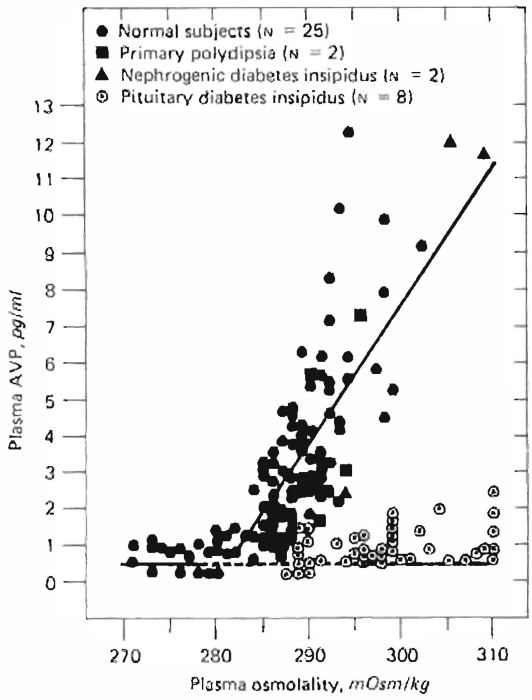


FIGURE 4

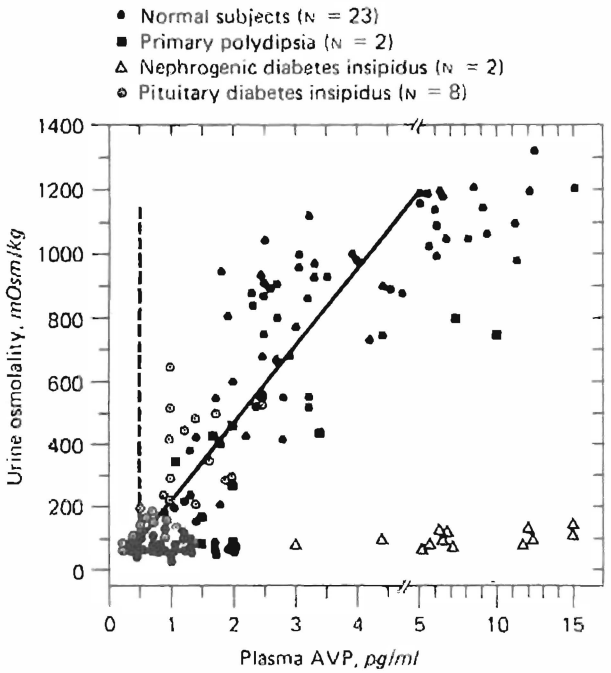


FIGURE 5

patients with psychogenic polydipsia will have low POSM due to expansion of ECV. After 8-12 hours of fluid restriction normal individuals and those with psychogenic polydipsia will increase urine osmolality to minum of 800 M OSM. Patients with central DI will have varying degrees of subconcentration depending on the amount of ADH available. Response to pitressin will distinguish between nephogenic DI and central DI.

Polyurea should be managed according to its etiology. For central diabetes insipidus this is pitressin by injection or nasal spray, and oral antidiuretic agents. Pitressin injection has unpredictable response and frequently leads to hyponatremia if over used. Synthetic vasopressin nasal spray is tolerated much better, however, it is poorly asorbed by patient with nasal allergy and mucosal edema. Both forms may be cardiac vasoconstrictive and also may lead to antibody formation leading to decreased effectiveness.

Oral antidiuretic agents are not only more effective and convenient (easy) to administer but also have less side effects. They include clofibrate, chlorpropamide and carbamazepine. None of them is effective in lowering urine output in normal persons, nephrogenic DIL, psychogenic polydipsia or complete (Type I) DI (no ADH). Addition of thiazide diuretic, reduces urine output by producing negative sodium balance GFR. We are in the process of reporting our experience with 30 patients with central DI on oral antidiuretic agents. Here we present data on 3 such patients as preliminary report. Two of these patients had idiopathic DI, and one post hypophysectomy DI. Their fluid intake, urine output, urine and plasma osmolality are shown in Table 6, 7, 8. Plasma AVP was measured by radioimmunoassay as described earlier (ref. 1).

We conclude that, both clofibrate in dose of 2-3 GM/day and chlorpropamide in dose of 500 MG/day are effective in lowering urine output from 50-80%. Clofibrate alone is less effective than chlorpropamide, however, when either of them was combined with chlorthiazide 500 MG daily, there was further reduction in urine output. By 3rd-4th day of the combined treatment metabolic balance was achieved.

There was appropriate increase in urine osmolality. Plasma osmolality fell to normal suggesting that the anti diuretic effect of these agents was not due to

PATIENT 1, TABLE 6

TREATMENT OF PITUITARY DIABETES INSIPIDUS WITH ORAL AGENTS

Hosp. Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14
O.C. Idiopathic	Rx	NONE			2 GM		ATROMID-S 3 GM				ATROMID 3 GM + DIURIL 0.5GM DAILY				
Intake L/Day		10.36	14.39	13.49	10.13	9.43	6.86	5.00	5.09	5.45	4.23	4.11	3.28	2.99	2.17
Output L/Day		12.85	13.11	12.70	11.30	11.60	5.30	5.15	6.08	6.00	4.28	4.13	3.30	1.96	1.76
U. OSM Mosm/Ks		95	67	61	96	112	172	158	160	175	242	297	343	428	450
P. OSM Mosm/Kg		296	307	295	295	300	294	292	292	293	290	289	285	282	282
P ADH Pg/ml		<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5	<0.5

PATIENT 2, TABLE 7

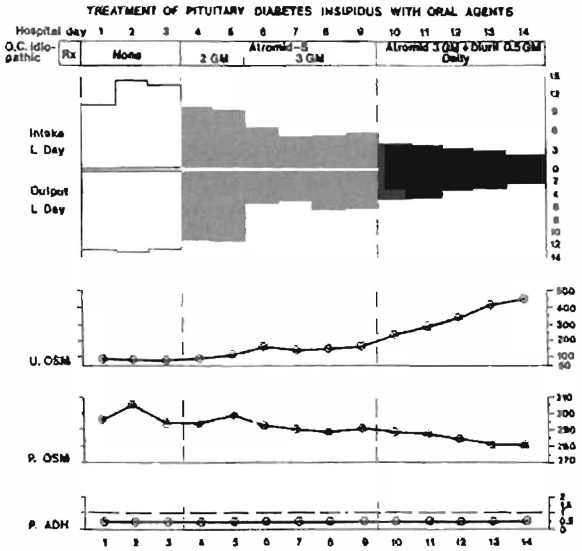
TREATMENT OF PITUITARY DIABETES INSIPIDUS WITH ORAL AGENTS

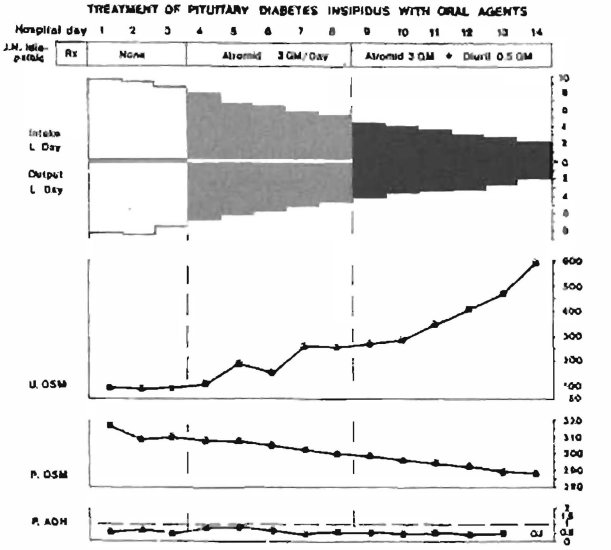
Hosp. Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14
M.C. Post Hypo	Rx	NONE				DIABINESE 500 MG DAILY				NONE		CLOFIBRATE 2 GM/DAY (Atromid-s)			
Fluid Intake L/Day		4.08	5.24	3.93	5.05	3.95	2.10	2.31	1.75	4.05	4.44	2.90	2.78	2.71	2.70
Urine Output L/Day		5.15	5.36	5.14	5.28	3.88	2.90	1.94	1.78	3.51	3.35	1.71	1.69	1.98	2.00
U. OSM Mogm/Kg		176	167	152	156	221	263	335	407	195	203	376	370	365	543
P. OSM Mosm/Kg		303	296	297	299	---	295	293	291	302	302	300	298	296	294
P. ADH Pg/Ml		0.5	0.5	0.5	0.5	---	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

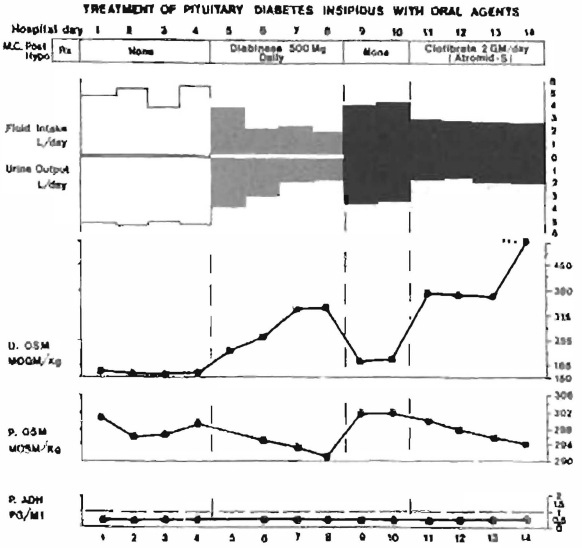
PATIENT 3 FIGURE 8

TREATMENT OF PITUITARY DIABETES INSIPIDUS WITH ORAL AGENTS

Hosp. Day		1	2	3	4	5	6	7	8	9	10	11	12	13	14
J.N. Idiopathic	Rx	NONE			ATROMID 3 GM/DAY					ATROMID 3 GM + DIURIL 0.5 GM					
Intake L/Day		9.58	9.20	8.50	7.82	6.44	6.40	5.60	5.12	4.26	3.80	3.65	3.00	2.80	2.10
Output L/Day		8.35	8.80	7.80	6.90	6.15	5.80	5.20	4.60	4.10	3.40	3.30	3.10	2.60	2.00
U. OSM Mosm/Kg		96	80	86	120	191	154	260	258	270	284	350	410	474	2590
P. OSM Posm/Kg		316	308	310	308	307	305	303	300	298	296	295	293	290	288
P. ADH Pg/ml.		0.6	0.7	0.5	0.8	0.9	0.7	0.5	0.6	0.5	0.5	0.6	0.5	0.5	OJ







increase in AVP secretion but rather on the renal tubular level. This was confirmed by AVP level measured by radioimmunoassay which was low in these patients with central DI before and did not increase after treatment with oral agents. We recommended clofibrate 2 to 3 GM with chlorthiazide 500 MG. daily in the management of central diabetes insipidus. We noted no side effects of clofibrate; however patients with thiazide diuretics should be observed and treated for hypokalemia.

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