Psychotropic-induced Water Intoxication and Its Countermeasures

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Abstract: The incidence of polydipsia and water intoxication is high in psychiatric patients. We studied the status of water intoxication among 4,882 in-patients, mostly of psychiatry hospitals. The subjects were 58% men, 42% women, mean age 53.6, and 72% of them were diagnosed as schizophrenia and related disorders. Using the polydipsia behavior assessment scales developed by us, we found polydipsia approximately 20% of the subjects. As for clinical factors related to polydipsia, a significant number of polydipsia patients were found among men and smokers, and also a significant number of patients diagnosed as schizophrenia, mental retardation or epilepsy. As for the relation to the drug therapy, polydipsia patients received significantly higher doses of antipsychotics compared to non-polydipsia patients. Anti-epileptics and anti-parkinsonism agents were more frequently used in the polydipsia patients. When serious cases among these polydipsia patients were defined as "pathological polydipsia", there were, however, no difference in the antipsychotic doses between the pathological and the non-pathological polydipsia patients. It was concluded that while the drug therapy is highly relevant to development of polydipsia, other factors were more relevant in serious cases.

Key words: Water intoxication; Psychotropics; Excessive water consumption; SIADH

Introduction

Within the daily clinical milieu in psychiatry, patients who consume large quantities of water are often observed to develop disturbance of consciousness or seizure due to hyponatremia. This phenomenon is described as water intoxication.

Development of water intoxication is discussed often in relation to treatment with psychotropics, but the incident was first reported in 1930s prior to development of psychotropic agents. For instance, Hopkins and Sleeper *et al.* measured the daily urine quantities of 92 schizo-

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Table 1 Past Reports on Polydipsia and Polyuria

Author	Jose & Perez-Cruet	Blum *et al.*	Lawson *et al.*	Okura and Morii	Vieweg *et al.*	Evenson *et al.*	Godleski *et al.*	Bremner and Reagan	Matsuda	Nakayama *et al.*
Year reported	1979	1983	1985	1986	1986	1987	1988	1991	1992	1995
No. of cases	239	241	S:35 non-S:7 N:31	225	103	2,201	34	877	247	2,252
Country	USA	USA	USA	Japan	USA	USA	USA	UK	Japan	Japan
Incidence (%)	6.6	17.5	S:20	3.1	39	6.2	59	3.5	20	12.0
Mean age			S:30.9 non-S:32.1 N:33.5		M:37.6 F:47.0	PD:50.9 All:60.3	All:36.4 PD:34 non-PD:40	PD:42 All:49	41.9	
Risk factors		(smoking)	schizo-phrenia			schizo-phrenia (female)		schizo-phrenia (male)		

S: schizophrenia, non-S: nonschizophrenic patients, N: normal controls, PD: polydipsia, non-PD: non-polydipsia
M: male, F: female

phrenic patients and reported that the quantities were about twice as much as those of healthy persons. Table 1 lists past reports concerning polydipsia and polyuria.

As the causes for water intoxication, SIADH (Syndrome of inappropriate secretion of antidiuretic hormone) which is abnormal secretion of ADH (anti-diuretic hormone), side-effects of psychotropics, and morbid conditions of psychosis are suggested, but no definite conclusion has so far been drawn. This paper focuses on the result of the largest ever scale study conducted on about 5,000 patients supervised by Prof. Kamijima of Showa University Faculty of Medicine, with particular emphasis on the clinical features of polydipsia and water intoxication and its countermeasures.

Clinical Picture of Polydipsia and Water Intoxication

In view of the high prevalence of water intoxication among psychiatric patients, with some cases culminating in death, many studies have so far been conducted. However, there are so far no definition agreed by the researchers of this area and several terms such as "psychogenic polydipsia" and "compulsive water drinking" are used.

In the present study, the patients observed to have any one of the signs including bodyweight gains of at least 3 kg/day, polyuria or incontinence, low specific gravity urea, and hyponatremia among those who have developed polydipsia were defined as showing "pathological polydipsia". The patients who developed the CNS symptoms such as disturbance of consciousness, seizure or vomiting were defined as suffering from "water intoxication".

1. Subjects

In our study, the subjects were 4,882 inpatients of 10 psychiatric hospitals and psychiatric wards of 2 general hospitals. The subject breakdown shows 58% of men, 42% women, mean age 53.6, and the average duration of illness was 24.6 years. Diagnostically, 72% were schizophrenia and related disorders, 11% had

Table 2 Evaluation Sheet for Polydipsia

A. Has the following behavior been observed <u>for two days or more in the last six months</u>? Please check the box.		
• Is seen always holding a glass in hand	☐ (1) Yes	☐ (2) No
• Stops at a faucet or a kettle with a glass in hand and continues drinking water	☐ (1) Yes	☐ (2) No
• Continues drinking water by having a bottle or glasses nearby	☐ (1) Yes	☐ (2) No
• Drinks water directly from the faucet	☐ (1) Yes	☐ (2) No
• Frequency and intake amount of coffee or soft drink are enormous	☐ (1) Yes	☐ (2) No
• Drinks water frequently within the day	☐ (1) Yes	☐ (2) No
• Continues drinking water by disregarding an order not to drink so much	☐ (1) Yes	☐ (2) No
• Gets angry and resists an order not to drink so much	☐ (1) Yes	☐ (2) No
• Drinks water secretly at places such as toilet or wash basin which are not normal drinking places	☐ (1) Yes	☐ (2) No
• Drinks a lot of water in one gulp	☐ (1) Yes	☐ (2) No
• Drinks soiled water from toilet, urine, or water from puddle	☐ (1) Yes	☐ (2) No
• Volunteers information that he/she is drinking lots of water including soft drinks	☐ (1) Yes	☐ (2) No
B. During the last six months, was prevented from drinking lots of water by having been forced to deposit the glass or bottle with the staff, was placed in an isolation ward, or was restrained the amount of drinking water	☐ (1) Yes	☐ (2) No
If <u>yes</u> → ☐ Check the amount of water drinking	☐ Restrain the amount of water drinking	
☐ Force to deposit the glass or bottle with staff	☐ Check the amount of urine	
☐ Place in the protective ward	☐ Others ( )	

organic psychotic disorders, 4% each had either of mental retardation, alcoholism, drug dependence, or maniac-depressive psychosis.

Twelve items regarding polydipsia behavior of the subjects were studied. As shown in Table 2, polydipsia was defined if a patient showed at least one of the 12 items of the Table 2.

2. Polydipsia and clinical factors

The study revealed approximately 20% of subjects ($n = 972$) were polydipsia. Polydipsia is found in significantly more men and smokers and that it is highly prevalent among patients of schizophrenia (21%), mental retardation (31%), and epilepsy (33%).

Since the definition of polydipsia is not necessarily consistent in previous studies, direct comparison with the present study is difficult. However, many studies cited "male gender", "smoking", "schizophrenia", and "mental retardation" as clinical factors related to polydipsia, which are similar to the result of the present study.

3. Polydipsia and psychotropics

Antipsychotic doses were expressed as chlorpromazine equivalent, and its relation with polydipsia was studied. In the high antipsychotic dose groups, polydipsia was observed at a high incidence. When the daily antipsychotic doses of the groups with and without polydipsia were compared, the dose was significantly higher in the polydipsia group (1,281 mg chlorpromazine equivalent) than in the non-polydipsia group (930 mg chlorpromazine equivalent). A similar result was obtained when the subjects were limited to schizophrenia patients (Fig. 1).

We then studied the relation between the types of psychotropics and polydipsia. There were significantly more polydipsia patients among those receiving anti-epileptic or anti-parkinsonism agents.

Because most of surveyed subjects were receiving plural psychotropics, logistic regres-

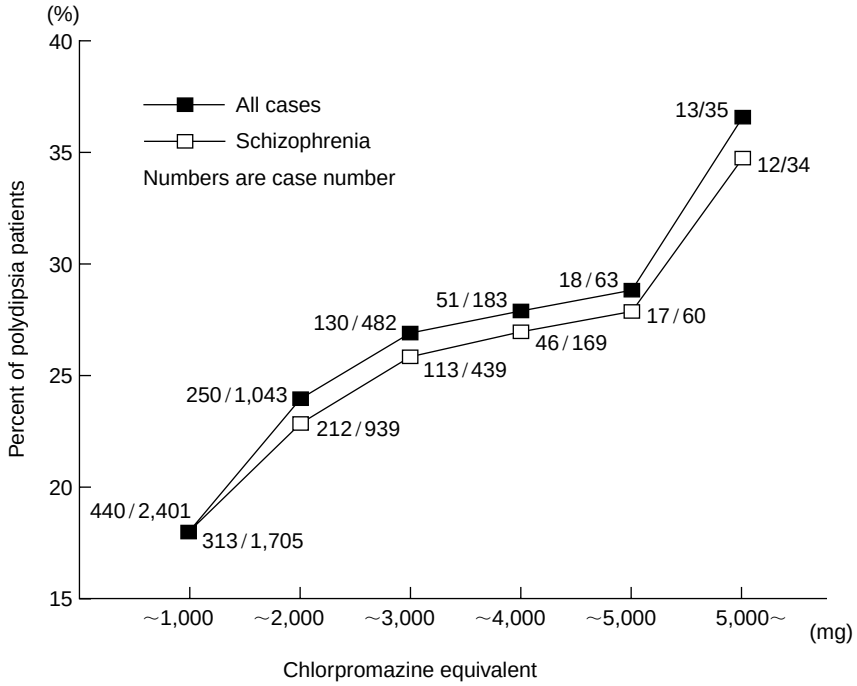

Fig. 1 Polydipsia and antipsychotic medication

sion analysis was conducted with psychotropic administration as a variable in order to evaluate effects of individual drugs. The result showed that polydipsia was likely to occur among significantly more of those receiving psychotropic medicine such as chlorpromazine, levomepromazine, propericyazine, perphenazine and zotepine, anti-epileptics such as phenytoin, anti-anxiety agents such as diazepam, hypnotics such as bromovalerylurea, and anti-parkinsonism agents such as promethazine.

No consistent conclusion has been drawn regarding the relation between polydipsia and drug therapies. While there are reports that psychotropic agents induce polydipsia and water intoxication, there are also studies that recognized the fact that polydipsia and water intoxication improved with improvement of psychiatric symptoms by the psychotropic therapy.

According to the present study, however, the incidence of polydipsia is higher if the antipsychotic dose is higher, and there is a significant relation between polydipsia and drugs such as phenothiazines. It is therefore desirable to reduce the psychotropic dose as much as possible by substitution with other drugs in order to prevent polydipsia, particularly that of phenothiazine with its intense sedation effect, during the chronic phase.

Although previous reports point out the risk of drugs other than psychotropics such as carbamazepine, thiazide, tolbutamide, no consistent view has been presented.

One of the mechanisms by which water intoxication develops by psychotropics is probably abnormal ADH secretion. There are reports that psychotropics such as chlorpromazine, fluphenazine, and thioridazine, anti-depressants such as imipramine and amitriptyline, and anti-epileptics such as phenytoin and carbamazepine promote ADH secretion. However, another report suggests that abnormality of the ADH regulation system is due to psychosis itself. While the effects of psychotropics on development of polydipsia and water intoxication cannot be denied, the morbid conditions *per se* of

the disease are believed to be relevant, warranting further studies.

4. Pathological polydipsia and water intoxication

As discussed above, 972 or approximately 20% of 4,882 psychosis patients were found with polydipsia.

Those who were observed to have gained at least 3 kg / day of bodyweight or to have developed polydipsia or incontinence, low specific gravity urea or hyponatremia in the six months previously were defined as "pathological polydipsia", and those whose polydipsia was accompanied with the CNS symptoms such as disturbance of consciousness, seizure or vomiting were defined as "water intoxication".

Pathological polydipsia was found in 45% of polydipsia patients and water intoxication in 3% of polydipsia patients. Compared to reports of other institutions, the incidence of water intoxication was rather low, but this may be attributable to the fact that only the serious cases were selected as water intoxication according to the definition employed in this study.

Polydipsia patients were then divided into two, pathological polydipsia and non-pathological polydipsia, and the relation between pathological polydipsia and clinical factors was studied. In comparison of pathological polydipsia patients and non-pathological polydipsia patients, no significant difference was seen in terms of gender or smoking. As for diagnosed disease entities, the incidence rose in the order of epilepsy, mental retardation, and schizophrenia.

We then studied the relation between the psychotropic therapy and pathological polydipsia. The daily dose of antipsychotics was significantly higher in the pathological polydipsia group than in non-pathological group. However, when a similar comparison was made among those administered antipsychotics in the pathological polydipsia group, the difference was not significant. By logistic regression analysis, the factors related to pathological polydipsia were sought. Significant explanatory variables were the age at the onset, smoking, schizophrenia and, amobarbital.

In view of the above result, it was concluded that while psychotropics are significantly related to development of "polydipsia", their effects are limited, suggesting that other factors do participate in serious or chronic polydipsia.

Countermeasures for Polydipsia and Water Intoxication

Because of the poor understanding of pathophysiology of polydipsia and water intoxication, we are currently compelled to rely on the nosotropic treatment. In absence of radical treatment, it is necessary to detect polydipsia early, to prevent progress to serious water intoxication, and to treat hyponatremia early if water intoxication is discovered, so that progression to grave, life-threatening conditions accompanying disturbance of consciousness or seizure may be prevented.

As for prevention of polydipsia, patients should be placed under surveillance by checking and controlling the amount of water they drink, having them deposit their glasses and bottles of water with the staff, measuring the amount of urine and restricting activities by the use of the seclusion room.

When polydipsia is detected by observation of the daily water drinking behavior and bodyweight measurement, serum sodium level and osmotic pressure, the specific gravity of urine and osmotic pressure should be measured frequently and the degree of water retention be learned. Patients whose diurnal bodyweight changes are excessive are likely to be ingesting excessive quantity of water, and if their water intake is adequately controlled, their chances of developing water intoxication may be prevented.

The CNS symptoms due to hyponatremia appear generally when the serum sodium level rapidly lowers. In the case of water intoxication patients, they often do not develop symptoms even when their serum sodium level has gone down below 120. If the CNS symptoms such as

seizure or disturbance of consciousness appear, drip infusion of physiological saline or hypertonic saline solution is necessary.

Such behavioral measures as well as the review of drug therapy are necessary for prevention of polydipsia and water intoxication. It is clear from our data mentioned above that various psychotropics are one of the causes that induce polydipsia. The psychotropic doses should be decreased as much as possible by considering the mental conditions of patients, and concurrent dosing of multiple drugs should be avoided so that water intoxication may be prevented.

In recent years, it is pointed out that some drugs may possibly be effective for treatment of polydipsia and water intoxication. There are reports that propranolol, naloxone, and angiotensin converting enzyme antagonists are effective for treatment of polydipsia as well as demeclocycline with its anti-ADH activity, and the combined use of lithium and phynytoin is also effective for hyponatremia. Clozapine, a antipsychotic for atypical psychosis, is also reported to be effective for hyponatremia. All these reports warrant further studies.

Conclusion

As polydipsia and water intoxication are often encountered in clinical psychiatry and could be sometimes life threatening, adequate diagnosis and countermeasures are necessary.

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