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Are psychotropic drugs involved in gallstone-induced acute abdomen in inpatients with schizophrenia?

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Acute abdomen in patients with schizophrenia is a life-threatening complication, and intraoperative and postoperative management are difficult [1]. In the past five years, we had 18 patients undergo emergency operations due to acute abdomen during hospitalization for the treatment of schizophrenia. The causative diseases of acute abdomen in these patients were: gallstones in 12 patients, perforated appendicitis in 3 patients, ileus due to ingested foreign bodies in 1 patient, abdominal compartment syndrome in 1 patient, and acute gastric dilatation in 1 patient. Therefore, gallstones were the cause of the acute abdomen in the overwhelming majority of these patients.. However, not every gallstone causes acute abdomen, and the number of patients with silent gallstones is much larger [2]. We therefore conducted a case-control study on whether psychotropic drugs are associated with gallstones and acute abdomen in inpatients with schizophrenia.

The period of this study was 5 years, from April 2005 to March 2010. Case group 1 consisted of 12 inpatients with schizophrenia who developed acute abdomen due to gallstones and underwent emergency surgery during the study period (emergency surgery patients). Case group 2 consisted of 33 inpatients with schizophrenia who were coincidentally found to have gallstones by ultrasonography during the study period (silent gallstone patients). For the control group, 50 patients were randomly selected from among 521 patients who were in the hospital for schizophrenia during the study period, and of the 50 patients, 36 who consented to abdominal ultrasonography and were then found to not have gallstones were assigned to the control group. We examined sex, age, body mass index (BMI), illness duration, chlorpromazine equivalent dose for the antipsychotic drugs, biperiden equivalent dose for the antiparkinsonian drugs, diazepam equivalent dose for the anti-anxiety drugs, total cholesterol level, triglyceride level, and fasting blood sugar level in each group. Groups were compared using non-repeated measures ANOVA followed by Bonferroni correction, and the Yates Chi-square test where applicable, with $p < 0.05$ indicating a significant difference. The values were expressed as the mean ± standard deviation. The results are shown in Table 1.

The ages and illness durations of patients with gallstones needing emergency surgery and those with silent gallstones exceeded those of the control group. Silent gallstones were highly prevalent among female schizophrenia patients. These results were consistent with the high prevalence of gallstones in middle-aged and older women [2]. However, because no differences between the sexes were seen in the gallstone group that received emergency surgery, this suggested that men might be more likely than women to require emergency surgery due to gallstones. No differences among the groups were found in BMI, cholesterol, triglyceride, or blood sugar levels.

The chlorpromazine equivalent doses in the gallstone group that received emergency surgery and the silent gallstone group were much larger than those in the control group. Therefore, the doses of antipsychotic drugs appeared to be a risk factor for gallstones. Inpatients in psychiatric hospitals have a high prevalence of gallstones (two or three times that in the

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general population), and it has been reported that the long-term administration of antipsychotic drugs is associated with gallstone formation [3], although the mechanism is still unknown. The doses of the antiparkinsonian and anti-anxiety drugs in the gallstone group that received emergency surgery were much larger than those in the silent gallstone group. Severity of cholelithiasis leading to acute abdomen was not associated with the chlorpromazine equivalent dose but was associated with the biperiden and diazepam equivalent doses. One possible mechanism is the passage of enterobacteria into the biliary tract from the duodenum by anticholinergic action, resulting in concomitant cholecystitis. Moreover, a common problem with schizophrenia patients is that their insensitivity to pain delays the diagnoses of diseases requiring surgery [4]. The sedative effects of anti-anxiety drugs may mask pain response, an inherent defense mechanism of the body, allowing gallstone-induced cholecystitis to progress silently, leading to delayed diagnosis and the onset of acute abdomen. Aside from the influence of psychotropic drugs, however, negative and cognitive symptoms may play an important role in acute abdomen and gallstone formation in schizophrenia patients due to their problematic dietary habits and relative lack of physical exercise.

Table 1. Baseline Characteristics

	Case group 1 (acute abdomen with gallstones)	**Case group 2** (silent gallstones)	**Control group**	P value
Number of subjects	12	33	36	
Age (years)	62.8 ± 7.1*	65.8 ± 6.9*	49.2 ± 14.8	P < 0.05
Sex (male/female)	6 / 6	5 / 28*	18 / 18	P < 0.01
BMI	24.5 ± 3.7	25.9 ± 3.4	23.9 ± 3.1	NS
Illness duration (years)	31.9 ± 6.9*	29.5 ± 5.1*	20.0 ± 10.2	P < 0.05
Chlorpromazine equivalent (mg/day)	1147.1 ± 333.8*	1027.6 ± 310.3*	645.9 ± 217.1	P < 0.01
Biperiden equivalent (mg/day)	5.3 ± 2.0*†	2.7 ± 1.4	1.9 ± 1.3	P < 0.05
Diazepam equivalent (mg/day)	14.1 ± 5.2†	4.3 ± 2.9	6.1 ± 3.2	P < 0.05
Total cholesterol (mg/dL)	196.8 ± 19.4	182.2 ± 42.5	174.0 ± 41.2	NS
Triglyceride (mg/dL)	148.3 ± 44.8	135.5 ± 31.5	138.3 ± 30.4	NS
Fasting blood sugar (mg/dL)	94.3 ± 8.9	96.9 ± 9.2	97.8 ± 11.2	NS

*: significantly different from control group
†: significantly different from silent gallstone group
NS: not significant

In the present study, the use of large doses of antipsychotic, antiparkinsonian, and anti-anxiety drugs was determined to increase the risk of gallstone-induced acute abdomen. Therefore, treatments that emphasize the use of optimal minimum doses of each drug are required. One limitation of the present study is that it was retrospectively conducted. The association between psychotropic drugs and acute abdomen needs to be studied prospectively.

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