Comparative Study of the Effectiveness of Zuclopenthixol Acetate and Haloperidol in Acutely Disturbed Psychotic Patients

UNCHULEE TAYMEEYAPRADIT, M.D.*,
SURACHAI KUASIRIKUL, M.D.**

Abstract

Objectives : To study the effectiveness, frequency of administration and side effects of zuclopenthixol acetate (ZPTA) and haloperidol (HAL) in the treatment of acute psychotic disturbance with aggression.

Method : Purposive sampling method was employed in a group of psychotic patients with aggression admitted to Songkla Neuropsychiatric Hospital, they were randomly divided into 2 groups: ZPTA group and HAL group. All of the patients were evaluated daily for 7 consecutive days using the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression Scale (CGI). Statistical analysis was performed by using the Student *t*-test and Linear regression.

Results : There were 70 patients with diagnosis of schizophrenia, mania and acute psychosis. Thirty-eight patients were randomly assigned to the ZPTA group and were given 50-100 mg of the drug, while 32 patients received HAL 5-10 mg. The result showed a significant reduction in BPRS or CGI scores in both groups. Patients treated with ZPTA required less frequent administration than did those on HAL ($p < 0.05$). There was no statistically significant difference in the reduction in scores between the two groups. Nor was there a statistical difference in reduction of aggression based on BPRS rating. Each group of patients showed a few side effects of mild degree.

Conclusion : Both ZPTA and HAL were effective in the treatment of acute psychosis with aggression, but frequency of administration was lower in the ZPTA group

Key word : Effectiveness, Aggression, Acute Psychosis, Zuclopenthixol Acetate, Haloperidol

TAYMEEYAPRADIT U & KUASIRIKUL S
J Med Assoc Thai 2002; 85: 1301-1308

* Psychiatric Division, Songkla Neuropsychiatric Hospital, Songkhla 90000,
** Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Acutely disturbed psychotic patients with aggressive behavior often do not acknowledge that they are ill. Verbal intervention is frequently ineffective and cooperation in taking oral medication may be poor. Parenteral administration of medication to control the behavior and obtain tranquility is, therefore, usually needed in the early period of treatment (1). Currently available injectable antipsychotic drugs such as haloperidol and chlorpromazine are short-acting with effects lasting about 4-6 hours(2). This means they have to be frequently administered causing a problem in treating uncooperative patients(1,2). The results of recent research support the role of benzodiazepines-lorazepam and clonazepam- in the achievement of rapid tranquilization in acutely disturbed violent patients(3-6). Frequent administrations of aqueous solution of chlorpromazine and haloperidol have the potential disadvantage of causing tissue damage at the injection site(7,8).

Frequent administration is a major problem in the management of acutely disturbed, uncooperative aggressive patients. In these patients, a reduction in frequency of drug administration may increase cooperation and lead to a better outcome. The medication given should have rapid onset, be long-acting and have minimal side effects.

Reports of pharmacokinetic studies(9,10) and various open and double-blind controlled trials have shown that zuclopenthixol acetate (ZPTA) has a rapid onset of action with effects lasting about 72 hours with few side effects(11-18).

Chouinard et al(11) performed a double-blind controlled study of parenteral ZPTA given in a dose of 50-150 mg every 3 days (average dose of 117.6 mg/day) and oral HAL (average dose of 18.9 mg/day) in 40 acutely disturbed patients. The patients were evaluated with the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impression (CGI) scale during the first 6 days of treatment. The results showed no statistical difference in antipsychotic or extrapyramidal effects. However, ZPTA had a higher sedative effect and caused a slight elevation of serum creatinine phosphokinase level.

Matar et al(12) studied 15 patients with acute psychosis with 75-100 mg of ZPTA on the first day of treatment, The patients were evaluated 72 hours post treatment with the Clinical Global Impression, Brief Psychiatric Rating and Bech-Rafaesen Mania scales. A significant reduction in rating score was obtained after a single injection of ZPTA. Patients became peaceful with a reduction of hostility, tension and excitement. Side effects were minimal.

Amdisen et al(13) performed a study on 83 acutely disturbed, hospitalized psychotic patients who received a ZPTA injection of 50-150 mg/day. BPRS scores obtained on day 6 of treatment were statistically lower than those of day 1. Patients with mania showed a score reduction of 57 per cent while those with chronic psychosis with an acute exacerbation of their symptoms showed a reduction of 50 per cent. The drug effect lasted 2-3 days. There were a few extrapyramidal side effects but were of a mild degree.

Baastraup et al(14) carried out an open randomized multi-center trial in 169 psychotic patients. The patients were observed during the first 6 days of parenteral treatment with either 50-200 mg ZPTA (1-4 injections), 5-10 mg HAL (1-26 injections) or 10-20 mg ZPTA (1-22 injections). There was no statistical difference in reduction of BPRS and CGI scores between the groups. However, patients treated with HAL showed a higher incidence of hypokinesia during the first 24 hours of treatment.

Heikkila et al(15) carried out a double-blind, multi-center study in 49 hospitalized patients with acute psychosis or an exacerbation of chronic psychosis. Clinical assessments, including those on the BPRS, CGI, and UKU-side effects scale were done at baseline and after 1, 2, 4, 6, and 8 weeks of treatment with either ZPTA or HAL. The average daily doses at week 4 were 10.3 mg and 33.5 mg, respectively. Both treatments caused a significant reduction in scores with no between-group differences. There was a trend towards a slightly more rapid onset of effect and a somewhat stronger anxiolytic - antidepressant effect caused by ZPTA than to HAL.

Tan et al(16) studied 19 acutely disturbed, aggressive psychotic patients treated with an injection of 50-mg ZPTA. They were evaluated using the BPRS and there was a significant decrease in score at day 3 compared with day 1.

No systemic study of ZPTA has been carried out in Thai subjects. Differences in culture, norm, values in Thailand from Western countries and one study showed that serum levels of inactive trans-isomer of clopixol in Asians were higher than those of Caucasians. The authors, therefore, decided to study the effect of parenteral ZPTA administration in acute psychotic patients in a Thai population. Such a study

could yield information regarding efficacy and the required dosages of ZPTA compared with those of standard antipsychotic drugs, such as haloperidol.

Objectives

1. To compare the effectiveness of zuclopenthixol acetate and haloperidol in acutely disturbed psychotics during the first 7 days of parenteral treatment.

2. To compare the frequency of administration required for both drugs in such treatment

3. To study any side effects of parenteral ZPTA and HAL during the first 7 days of treatment

Method

A randomized controlled trial was carried out in psychotic patients admitted to Songkla Neuropsychiatric Hospital because of disturbed and aggressive behavior. The patients had not responded to verbal intervention. They were hospitalized for various lengths of stay between June 1997 and June 1998. The patients had diagnosis of acute psychosis, Schizophrenia with acute exacerbation, mania and other forms of psychosis. Purposive sampling technique was employed to yield a total of 70 patients.

Male and female patients between the age of 18 and 65 were included in the trial. They were diagnosed by a psychiatrist according to ICD-10 criteria (first episode, relapse or recurrence). All patients had a normal physical examination and normal laboratory results - blood urea nitrogen, creatinine and liver function test. Subjects with psychosis caused by medication or any medical condition and mentally retarded patients were not included in the study. Nor were patients who had received antipsychotic medications within the previous 14 days.

The Brief Psychiatric Rating Scale (BPRS) (19) and Clinical Global Impression (CGI) Scale were used. Quantitative measurements of tension, hostility, suspiciousness, uncooperativeness and excitement items in the BPRS were performed by a psychiatric nurse who was specially trained for this task and not informed of the medication received by the patients. Each patient was evaluated prior to the first dose of medication and then daily for 7 days.

An attending psychiatrist (U.T) drew lots to determine whether a patient would receive ZPTA 50-100 mg or HAL 5-10 mg. The frequency of doses was determined by one of the authors and was based on the severity of psychotic symptoms. Some patients also received other oral antipsychotic and mood stabilizing agents for the treatment of their underlying disorders.

Parenteral medication was repeated if the patient showed significantly disturbed and aggressive behavior after 6 hours of HAL or 12 hours of ZPTA. Side effects such as sedation, extrapyramidal symptoms and anticholinergic effects were evaluated by a psychiatrist by interview and physical examination.

Data analysis

The mean BPRS scores, ratings of aggressive behavior and CGI scores were analyzed for any statistical difference using the *t*-test and the Linear regression module of SPSS® program.

RESULTS

Demographic data

Details of demographic data of the patients are shown in Table 1.

Table 1. Characteristics of patients in ZPTA and HAL groups.

Characteristics	ZPTA group	HAL group
Number of patients	38	32
Sex (male : female)	24 : 14	17 : 15
Mean age (years)	29.90	30.50
Mean onset of acute episode (days)	13.63	20.09
Mean duration of illness (years)	4.4	4.76
Details of randomized patients :		
Schizophrenia with acute exacerbation	22	17
Acute psychosis, first episode	12	12
Bipolar disorder (Mania)	-	1
Other forms of psychosis	4	2
Mean BPRS score on day 1 prior treatment	86.71 (SD = 7.09)	87.16 (SD = 9.08)

Drug administration data

Details of drug administration in both patient groups are shown in Table 2. The difference in total frequency of administration in ZPTA and HAL groups was statistically significant (p = 0.004, 95% CI = -3.625 and -0.720).

Table 3 shows details of dosage administration. Table 4 shows relationship with BPRS score in each patient group. Dosage range of ZPTA administration in 7-day period was 50-500 mg 50 per cent of the patients received ZPTA at no more than a total of 100 mg. Dosage range of HAL administration in the 7-day period was 5-100 mg 50 per cent of the patients received no more than 15 mg of HAL.

Outcome of treatment

Table 5 shows the BPRS aggression scores in both groups. Statistical analysis showed that on Day-1 the score of ZPTA group was higher than that of HAL group (22.24 *vs* 19.97, $p < 0.05$). From Day-1 to Day-7, there was a reduction in aggressive score in both groups (22.24 *vs* 7.29 for ZPTA group and 19.97 *vs* 7.75 for HAL group) with an average aggressive score reduction in the ZPTA and HAL groups of 14.94 and 12.22 respectively. However, the score reduction in both groups showed no statistical difference (22.48-7.29 *vs* 19.97-7.75, $p > 0.05$).

Fig. 1 shows the reduction of BPRS scores with no statistical difference between the two groups (p = 0.425, 95% CI -2.863 and 6.718).

Fig. 2 shows a reduction in CGI scores with no statistical difference between the two groups (p = 0.874, 95% CI -0.266 and 0.312).

Further analysis on sub-groups of patients receiving ZPTA of 50-mg and 100-mg dose showed no statistical difference of BPRS reduction (p = 0.854, 95% CI -5.590 and 6.719) and CGI reduction (p = 0.152, 95% CI -0.118 and 0.734).

Table 2. Details of drug administration.

Characteristics	ZPTA group (N = 38)	%	HAL group (N = 32)	%
Patients receiving medication				
50 mg/dose ZPTA	25	65.8	-	
100 mg/dose ZPTA	13	34.2	-	
5 mg/dose HAL	-		31	96.9
10 mg/dose HAL	-		1	3.1
Frequency of administration in 7 days				
1-3 administrations	31	81.6	17	53.1
More than 3 administrations	7	18.4	15	46.9
Average total frequency of administrations in 7 days	2 SD = 1.92		5 SD = 3.67	

Table 3. Total dosages received during the 7-day period in each patient group.

Dose of ZPTA (mg)	Subjects receiving ZPTA (N=38)	%	Cumulative %	Dose of HAL (mg)	Subjects receiving HAL (N=32)	%	Cumulative %
50	10	26.32	26.32	5	9	28.12	28.12
100	14	36.84	63.16	10	4	12.50	40.62
150	2	5.26	68.42	15	4	12.50	53.12
200	4	10.53	78.95	20	2	6.25	59.38
250	2	5.26	84.21	25	2	6.25	65.62
300	3	7.89	92.11	30	2	6.25	71.88
350	1	2.63	94.74	35	1	3.12	75.00
450	1	2.63	97.37	40	2	6.25	81.25
500	1	2.63	100.00	45	1	3.12	84.38
				50	1	3.12	87.50
				55	2	6.25	93.75
				65	1	3.12	96.88
				100	1	3.12	100.00

Table 4. Range of dosage administration and related BPRS scores during the 7-day period of study.

	ZPTA group	HAL group
Minimum total dosage	50 mg	5 mg
Maximum total dosage	500 mg	100 mg
Day 1 minimum BPRS	69	68
Day 1 maximum BPRS	98	113
Day 7 minimum BPRS	31	32
Day 7 maximum BPRS	64	58

Two patients in the ZPTA group had mild tremor which was treated promptly and effectively with benzhexol. There was no inflammatory reaction at the injection site of ZPTA. The side effects of HAL included 7 cases of tremor (mild, 3 and moderate, 4). One patient with HAL had a reaction at the injection site which required an anti-inflammatory drug.

DISCUSSION

This study showed that parenteral ZPTA and HAL could be used in the initial (first 7 days) management of acutely disturbed aggressive psychotic patients with no difference in effectiveness between them. After 7 days of treatment there was a 50 per cent reduction in BPRS and CGI scores. These results are in accordance with the results of other studies (11-18). However, ZPTA-treated patients required less frequent administration of medication than those treated with HAL ($p < 0.05$). The average frequency of administration for ZPTA was twice daily and HAL five times a day. The use of ZPTA resulted in a cost

Table 5. Average scores of aggression from day 1 to day 7 in both patient groups.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
ZPTA group	22.24	17.53	14395	12.89	10.87	9.13	7.29
HAL group	19.97	16.38	13.94	11.97	10.69	9.25	7.75

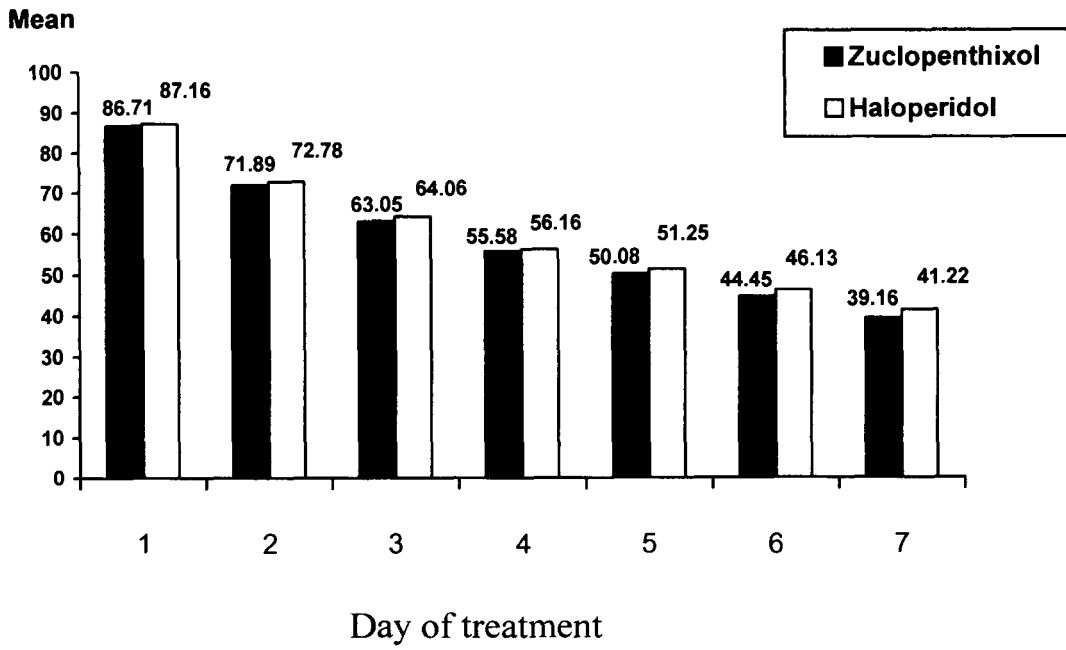

Fig. 1. Change in BPRS total scores with Zuclopenthixol acetate and Haloperidol.

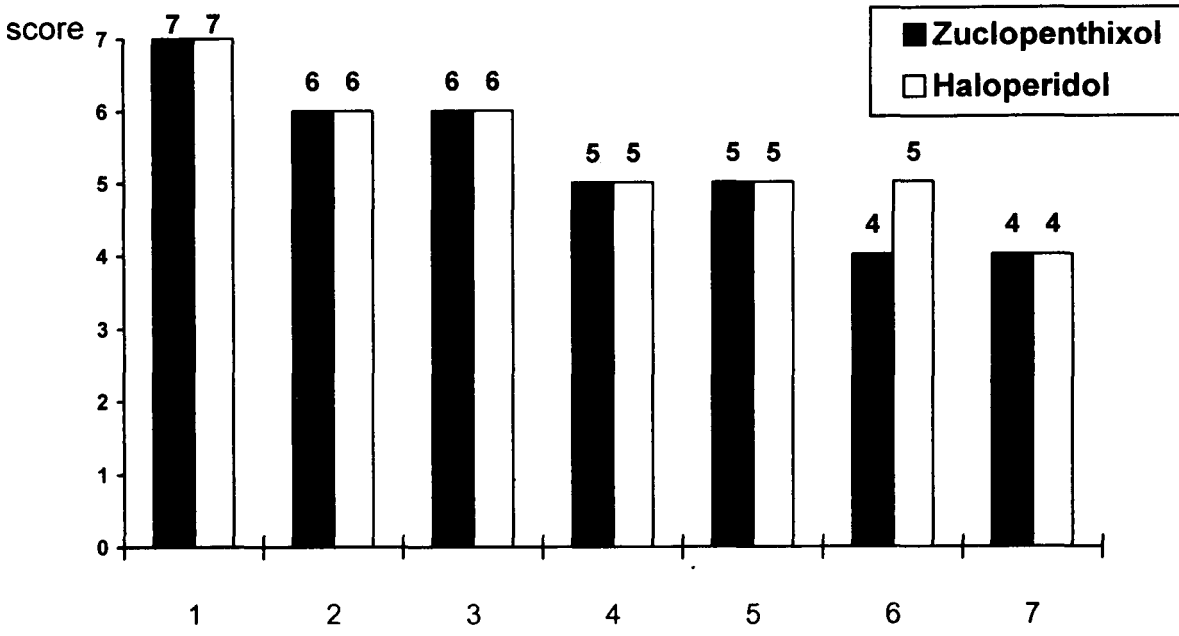

Fig. 2. Change in CGI total score with Zuclopenthixol acetate and Haloperidol.

saving over haloperidol in that it permits a 25 per cent reduction in nursing time care if 80 per cent of patients require 2 injections or less[20].

Neither group of patients showed severe side effects other than tremor. An inflammatory reaction at the injection site occurred more frequently in the HAL-treated group. The reason why ZPTA showed fewer side effects is probably because it is suspended in oil; this produces a slow release of drug into the circulation[9,10].

The present trial was carried out under close supervision in 70 in-patients with illnesses of various degrees of severity. Differences in the standard treatment the patients received and changes in the hospital setting might have contributed to the treatment outcome. Furthermore, both drugs showed differences in duration of action and required different frequencies of administration which might have interfered with the blind evaluation. Side effects were evaluated clinically. Since some patients did not cooperate well due to the severity of the drug effects, some side effects might not have been properly reported. Side effects were treated early; this also might have contributed to the low incidence of side effects recorded.

The reduction in aggression scores in the ZPTA group was higher than that in the HAL-treated group, but the difference was not statistically significant. Therefore, a study of a larger number of patients might be needed to determine whether ZPTA has greater effectiveness than HAL in the reduction of aggression.

Even though ZPTA is a potentially useful treatment in the management of acutely disturbed psychotic patients, more studies are needed to demonstrate whether ZPTA-treated Thai patients require lower doses of standard medication, shorter hospital stay or lower cost of care. If physicians consider patient autonomy, informed consent, the need to provide justice to all patients, and various causes of psychosis then the use of ZPTA for emergency treatment may only be justified under certain clinical circumstances. Its use is not appropriate as routine chemical restraint and requires protocols for appropriate use and monitoring[21].

(Received for publication on August 2, 2002)

REFERENCES

1. Tardiff K. Violence, in Textbook of Psychiatry, 3rd edit. Edited by Hales R, Yudofsky S, Talbott J. Washington DC: American Psychiatric Press, 1999: 1405-28.
2. Brizer D. Psyclopharmacology and the management of violent patients. Psychiatr Clin North Am 1988; 11: 551-68.
3. Chouinard G, Annable L, Tumier L, Holobow N, Szkrumelak N. A double-blind randomized clinical trial of rapid tranquilization with I.M. clonazepam and I.M. haloperidol in agitated psychotic patients with manic symptoms. Can J Psychiatry 1993; 38 (Suppl 4): S114-21.
4. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective emergency, department study. Am J Emerg Med 1997; 15: 335-40.
5. Bieniek S, Ownby R, Penalver A, Dominguez R. A double-blind study of lorazepam *versus* the combination of haloperidol and lorazepam in managing agitation. Pharmacotherapy 1998; 18: 57-62.
6. Dorevitch A, Katz N, Zernishlany Z, Aizenberg D, Weizmen A. Intramuscular flunitrzepan *versus* intramuscular haloperidol in the emergency treatment of aggressive psychotic behavior. Am J Psychiatry 1999; 156: 142-4.
7. Norteved H, Hojelse F. Repeated intramuscular injections of zuclopenthixol acetate and haloperidol-local tolerance at injection site, in Symposium for Dutch Psychiatrists. Copenhagen, Denmark, 1989: 3-10.
8. Svendsen O, Hojelse F, Bagdon RE. Tests for local toxicity of intramuscular drug preparations: Comparison of *in vivo* and *in vitro* methods. Acta Pharmacol Toxicol (Copenh) 1985; 56: 183-90.
9. Amdisen A, Aaes-Jorgensen T, Thomsen NJ, Madsen VT, Nielsen MS. Serum concentrations and clinical effect of zuclopenthixol in acutely disturbed, psychotic patients treated with zuclopenthixol acetate in Viscoleo. Psychopharmacology 1986; 90: 412-6.
10. Balant LP, Balant-Gorgia AE, Eisele R, Reith B, Gex-Fabry M, Garrone G. Clinical and pharmacokinetic evaluation of zuclopenthixol acetate in Viscoleo. Pharmacopsychiatry 1989; 22: 250-4.
11. Chouinard G, Safadi G, Beauclair L. A double-blind controlled study of intramuscular zuclopenthixol acetate and liquid oral haloperidol in the treatment of schizophrenic patients with acute exacerbation. J Clin Psychopharmacol 1994; 14: 377-84.
12. Matar AM, Abdel-Mawgoud M, Skov S. Zuclopenthixol: A new generation of antipsychotic drugs. An open clinical trial. J Clin Psychopharmacol 1990; 10: 283-6.
13. Amdisen A, Nielsen MS, Dencker SJ, et al. Zuclopenthixol acetate in Viscoleo-a new drug formulation. An open Nordic multicentre study of zuclopenthixol acetate in Viscoleo in patients with acute psychoses including mania and exacerbation of chronic psychoses. Acta Psychiatr Scand 1987; 75: 99-107.
14. Baastrup PC, Alhfors UG, Bjerkenstedt L, et al. A controlled Nordic multicentre study of zuclopenthixol acetate in oil solution, haloperidol and zuclopenthixol in the treatment of acute psychosis. Acta Psychiatr Scand 1993; 87: 48-58.
15. Keikkila L, Eliander H, Vartiainen H, Turunen M, Pedersen V. Zuclopenthixol and haloperidol in patients with acute psychotic states. A double-blind, mult-centre study. Curr Med Res Opin 1992; 12: 594-603.
16. Tan CH, Low BL, Ng LL, Khoo YM, Lee HS. Clinical evaluation and serum concentration of zuclopenthixol acetate in psychotic Asian patients: A single-dose preliminary study. Ther Drug Monit 1993; 15: 108-12.
17. Chakravarti SK, Muthu A, Muthu PK, Naik P, Pinto RT. Zuclopenthixol acetate (5% in 'Viscoleo'): Single-dose treatment for acutely disturbed psychotic patients. Curr Med Res Opin 1990; 12: 58-65.
18. Lowert AC, Rasmussen EM, Holm R, et al. Acute psychotic disorders treated with 5% zuclopenthixol acetate in 'Viscoleo' ('Cisordinol-Acutard'), a global assessment of the clinical effect: An open multicentre study. Pharmatherapeutica 1989; 5: 380-6.
19. Overall J, Gorham D. The brief psychiatric rating scale. Psycol Rep 1962; 10: 799-812.
20. Laurier C, Kennedy W, Lachaine J, Gariepy L, Tessier G. Economic evaluation of zuclopenthixol acetate compared with injectable haloperidol in schizophrenic patients with acute psychosis. Clin Ther 1997; 19: 316-29.
21. Fitzgerald P. Long-acting antipsychotic medication, restraint and treatment in the management of acute psychosis. Aust N Z J Psychiatry 1999; 33: 660-6.

เปรียบเทียบประสิทธิผลของยา Zuclopenthixol Acetate และ Haloperidol ในผู้ป่วยโรคจิตที่วุ่นวายก้าวร้าว

อัญชุลี เตมียะประดิษฐ์, พ.บ., สุรชัย เกื้อศิริกุล, พ.บ.***

วัตถุประสงค์ : เพื่อศึกษาเปรียบเทียบประสิทธิผล, ความถี่ของการใช้ยา และฤทธิ์ไม่พึงประสงค์ของยา Zuclopenthixol Acitate (ZPTA) และ Haloperidol (HAL) แบบฉีดในผู้ป่วยโรคจิตที่มีอาการวุ่นวายก้าวร้าว

วัสดุและวิธีการ : เลือกกลุ่มตัวอย่างแบบเจาะจง ได้กลุ่มตัวอย่างที่เป็นผู้ป่วยโรคจิตที่มีอาการวุ่นวายก้าวร้าว ซึ่งรับตัวไว้รักษาเป็นผู้ป่วยในของโรงพยาบาลประสาทสงขลา โดยวิธีการสุ่ม (randomization) แบ่งกลุ่มตัวอย่างเป็น 2 กลุ่ม โดยกลุ่มแรกได้รับ ZPTA และกลุ่มที่สองได้รับ HAL ประเมินอาการของผู้ป่วยก่อนได้รับยา และหลังได้รับยาใน 7 วันแรก โดยใช้ Brief Psychiatric Rating Scale (BPRS) และ Clinical Global Impression Scale (CGI) สถิติที่ใช้ Student *t*-test and Linear regression

ผล : กลุ่มตัวอย่าง 70 ราย เป็นจิตเภทโรคจิตทางอารมณ์ โรคจิตเฉียบพลัน และโรคจิตชนิดอื่น ๆ ได้รับ ZPTA ชนิดฉีด ขนาด 50-100 มิลลิกรัม จำนวน 38 ราย HAL ชนิดฉีด ขนาด 5-10 มิลลิกรัม จำนวน 32 ราย พบว่ามีการลดลงของค่าคะแนน BPRS CGI และความก้าวร้าวในทั้งสองกลุ่ม ซึ่งการลดลงของค่าคะแนนเหล่านี้แตกต่างกันอย่างไม่มีนัยสำคัญทางสถิติ แต่พบว่ากลุ่มที่ใช้ ZPTA มีความถี่ของการใช้ยาฉีดเพื่อสงบอาการน้อยกว่า กลุ่มที่ใช้ HAL พบฤทธิ์ไม่พึงประสงค์น้อย และไม่รุนแรงในกลุ่มตัวอย่างทั้งสองกลุ่ม

สรุป : ZPTA และ HAL มีประสิทธิผลไม่แตกต่างกันในการรักษาผู้ป่วยโรคจิตที่มีอาการวุ่นวายก้าวร้าว แต่ความถี่ในการฉีดซ้ำของ ZPTA น้อยกว่า HAL

คำสำคัญ : ประสิทธิผล, ความก้าวร้าว, โรคจิต, Zuclopenthixol Acetate, Haloperidol

อัญชุลี เตมียะประดิษฐ์, สุรชัย เกื้อศิริกุล
จดหมายเหตุทางแพทย์ ฯ 2545; 85: 1301-1308

* กลุ่มงานจิตเวช, โรงพยาบาลประสาทสงขลา, สงขลา 90000

** ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400