

Efficacy and safety of valproic acid versus haloperidol in patients with acute agitation: results of a randomized, double-blind, parallel-group trial

Shadi Asadollahi^a, Kamran Heidari^b, Hamidreza Hatamabadi^b, Reza Vafae^{c,d}, Somayeh Yunesian^b, Alireza Azadbakht^b and Ladan Mirmohseni^b

The objective of this study was to compare the efficacy of valproate versus haloperidol in decreasing the agitation level in affected patients in the emergency department. We assigned 80 acutely agitated patients to receive either intravenous sodium valproate (20 mg/kg) or intramuscular haloperidol (5 mg/1 ml). Agitation was measured at baseline and 30 min after the first injection using the Agitation–Calmness Evaluation Scale (ACES), the Positive and Negative Syndrome Scale-Excited Component subscale, and the Agitated Behavior Scale. For 80 patients treated with sodium valproate, the mean \pm SD dosage was 1541.5 \pm 286 mg (range 940–2400). The mean postintervention ACES scores from baseline to 30 min after drug injection were 4.73 (SD = 1.93) for the valproate group and 5.45 (SD = 2.09) for the haloperidol group ($P = 0.028$). No significant differences were observed in terms of the mean changes 30 min after the intervention for two additional agitation scales. A larger proportion of patients in the haloperidol group experienced intense sedation (36.2%,

$P < 0.001$) and extrapyramidal symptoms (8.7%, $P = 0.007$) compared with the valproate group (2.5% for intense sedation, no patient for extrapyramidal symptoms). The findings suggest that in the clinical practice setting of emergency psychiatry, intravenous valproate is as effective as haloperidol in reducing agitation, with a better safety profile. *Int Clin Psychopharmacol* 30:142–150 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

International Clinical Psychopharmacology 2015, 30:142–150

Keywords: agitation, haloperidol, psychotherapy, randomized-controlled trial, therapeutics, valproic acid

^aSchool of Medicine, ^bDepartment of Emergency Medicine, Imam Hossein Hospital, ^cSafety Promotion and Injury Prevention Research Center and ^dProteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran 17666-33815, Iran

Correspondence to Kamran Heidari, MD, Department of Emergency Medicine, Imam Hossein Hospital, Nezam Abad, Tehran, Iran
Tel: +98 912 134 16 75; fax: +98 21 775 570 69; e-mail: heidari-k@sbmu.ac.ir

Received 5 August 2014 Accepted 13 November 2014

Introduction

Psychiatric emergencies are critical situations with the risk of imminent harm toward affected patients, their family members and communities, and healthcare service providers (Kunen *et al.*, 2005). Psychiatric patients commonly present to emergency departments (EDs). Many of these patients are agitated, requiring treatment for their agitation in the ED (Cañas, 2007). Emergency physicians have to intervene quickly to reduce distress, protect both the patient and the hospital staff, and determine the etiology of the agitated behavior (National Collaborating Centre for Nursing and Supportive Care (UK), 2005).

Agitation is described as a disorganized and aimless psychomotor activity stemming from physical or mental discomfort (Lindenmayer, 2000). This can be seen in various clinical situations such as delirium, dementia, psychoactive substance intoxication/withdrawal, psychotic disorders (schizophrenia, delusional disorder), and mood disorders (bipolar disorder, major depressive disorder). Other conditions include anxiety disorder, acute reaction to stress, post-traumatic stress disorder, antisocial/borderline/paranoid personality disorder, autism, mental retardation, attention deficit hyperactivity

disorder, conduct disorder, and akathisia (Tesar, 1993; Lindenmayer, 2000). Given the wide range of clinical entities from which agitation may arise, it is among the most frequently encountered clinical problems in psychiatric facilities and hospital emergency services.

Physical restraints as a traditional intervention in the management of severe agitation can have deleterious physical and psychological influences on the patients and staff (Tesar, 1993). As an alternative to physical restraints, pharmacological restraint provides a logical humane choice and leads to rapid tranquillization without causing severe sedation (Dubin and Feld, 1989). Further advantages of rapid tranquillization include a decrease in the period of the agitated state, less time in seclusion and restraint, and a higher simplicity of evaluative procedures (Battaglia *et al.*, 1997).

There are few studies on the efficacy of several chemical modalities in the treatment of acutely agitated patients presenting to EDs. One of the most common methods of rapid tranquillization is the intramuscular (i.m.) administration of high-potency typical antipsychotics (haloperidol and droperidol), which are preferred by clinicians because of their effective delivery and rapid onset of effect (Janssen *et al.*, 1963). Their limitations are

well-known adverse events (AEs), including cardiac problems, intense sedative effect, extrapyramidal symptoms (EPS) (dystonia and akathisia), and anticholinergic side effects. The distressing adverse effects and the induction of intense sedation also interfere with the clinical diagnosis and are thus barriers for the future use of these classical therapeutic modalities (Pratt *et al.*, 2008).

During the past decade, valproic acid has been broadly investigated in a variety of clinical situations, such as migraine, anxiety disorders, seizure disorders, and controlling acute episodes of mania as a mood stabilizer. Valproic acid has a record of a low incidence of adverse effects and few drug–drug interactions (Lonergan *et al.*, 2004). Data on the antiagitation influence of such mood stabilizers are limited; more evidence on the mechanism of action is required to identify their function in a clinical setting. According to previous reports, the intravenous (i.v.) administration of valproate for acute agitation showed calming effects (Hilty *et al.*, 1998; Grunze *et al.*, 1999). Compared with haloperidol as a widely used antipsychotic agent, new treatment alternatives, such as valproate, can often restore a normal level of mental activity and thus normal level of verbal expression while keeping the patient awake (Sival *et al.*, 2002; Dolder and McKinsey, 2010).

To the best of our knowledge, valproate and haloperidol have not been compared in their effectiveness in reducing acute agitation. Therefore, we conducted a prospective, randomized, double-blind clinical trial to compare these agents in altering the agitation level and rate of AEs.

Materials and methods

Study design

The original study was a randomized, double-blind, parallel-group trial in which participants were assigned to receive valproate or haloperidol treatment. This investigation was carried out at the ED of a large metropolitan university-affiliated hospital with an average of 65 000 patient visits annually. The hospital supports a 4-year emergency medicine and psychiatry residency program and other specialties.

Participants

The study population included all adult patients (age range; 18–65 years) who were acutely agitated and required emergency parenteral pharmaceutical intervention for the control of violent behavior. Acutely agitated patients included those with violent, controlled, or uncontrolled muscular movement that placed both themselves and hospital staff in danger because of severely disruptive behavior. The classification of acute agitation patient was confirmed by a consultant attending emergency physician and a psychiatrist (24 h/day, 7 days/week).

Exclusion criteria were readily amendable causes for the agitation (hypoxemia or hypoglycemia), known hypersensitivity to either drug, hypotension (systolic blood pressure ≤ 90 mmHg), pregnancy or breastfeeding, known history of liver disease or uncontrolled diabetes, noticeable or suspected head trauma, a previous history of neuroleptic malignant syndrome, and seizure.

Hypoxemia was identified as an arterial oxygen saturation of 90% or less according to pulse oximetry measurements and hypoglycemia was defined as a plasma glucose level less than 50 mg/dl.

We obtained written informed consent from participants' caregivers or responsible family members who were present with the patients throughout the trial.

They were completely informed about the voluntary nature of participation and interventions. We excluded patients without a responsible family member at the time of agitation. After the resolution of the psychomotor agitation, written consent was also obtained from the patients. This study was approved by the Institutional Review Board and Ethics Committee of the Shahid Beheshti University of Medical Sciences. It was carried out in accordance with the Declaration of Helsinki of 2013.

Interventions

Physical restraint was initially used for severely agitated patients and then on the basis of the physician's discretion until no longer required. Peripheral i.v. access was established for all enrolled patients to collect blood samples for laboratory studies. Rapid serum glucose determination was performed for each patient using a glucose meter device. All patients were placed on standard hemodynamic monitoring.

We obtained a toxicology screen for all participants in both groups if the patients allowed the collection of urine samples.

Vital signs were also recorded both before the administration of medication and at 30 min after the intervention. According to the trial protocol, participants fulfilling the inclusion criteria were allocated randomly to either the i.m. haloperidol (5 mg/1 ml) plus i.v. placebo infusion (200 ml, normal saline) or the i.v. sodium valproate solution plus i.m. placebo treatment (1 ml, normal saline). The sedative solution for the valproate group was prepared by adding 200 ml distilled water to 20 mg/kg sodium valproate powder. The patients were continuously infused i.v. for 10 min. The doses were at the attending physicians' discretion, although the recommended initial dose for haloperidol administration is 2–5 mg, repeated as needed at 1-h intervals (Thomas *et al.*, 1992; Allen, 2000). If the patients continued to be agitated after the study drug was administered, a second dose could be administered at the discretion of the

treating attending physician. The study drugs were prepared in the same opaque syringe of equivalent volume by the Pharmacy Department of the center. The clinical safety of intervention was assessed by careful monitoring of AEs throughout the study. All AEs were reported directly to the principal investigators, who then decided whether the assigned intervention should be uncovered or the patient should be removed from the trial.

Outcome measures

The level of agitation/tranquilization was measured using an objective single-item agitation scale. The Agitation–Calmness Evaluation Scale (ACES) consists of an item scale with nine anchor points (1 = marked agitation, 2 = moderate agitation, 3 = mild agitation, 4 = normal, 5 = mild calmness, 6 = moderate calmness, 7 = marked calmness, 8 = deep sleep, 9 = unarousable) that provides rapid and accurate information on the primary state of agitation and transition into tranquilization after a pharmacological intervention (Lilly, 2004). We also used the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) and the Agitated Behavior Scale (ABS) scores. The PANSS-EC includes five items (excitement, tension, hostility, uncooperativeness, and poor impulse control) rated from 1 (not present) to 7 (extremely severe), yielding a potential maximum score of 35 points (Kay *et al.*, 1987). The ABS score is a valid scale that provides healthcare professionals with objective feedback on the course of a patient's agitation. It includes 14 clinician-rated items: attention-related behaviors, impulsivity/impatience, uncooperative behavior, violence/threats, unpredictable anger, self-stimulating behavior, resistance to restraint and intervention, wandering, restlessness, repetitive behaviors, loud/excessive talking, sudden changes of mood, excessive crying or laughter, and self-abusive behavior. All items are rated on the following four-point scale: 1 = absent; 2 = present to a slight degree; 3 = present to a moderate degree; and 4 = present to an extreme degree. Although this instrument was developed and is used primarily for the assessment of agitation in patients with cranial damage, it has been utilized for the assessment of agitation in patients admitted to the ED (Zun and Downey, 2008). The level of agitation was assessed at baseline and at 30 min after the administration of drugs. Differences between preintervention and postintervention scores were compared. All outcome assessments were performed blinded to treatment allocation. In all cases, randomization was performed by a trial administrator independent of raters and administering clinicians. The raters were psychiatrists who had previous experience with the psychiatric rating scores, especially measures of aggressive behavior and agitation or with the training or certification videotapes. The research assistant, administering clinicians, patients, caregivers, and raters were all blinded to the treatment assignment.

Randomization

Randomization was performed according to a computer-generated random numbers list. The trial instruction and data form for each treatment were sealed in a numbered

opaque envelope. An equal number of haloperidol and valproate envelopes were provided and placed in the study pack. As determined by the randomization list, each study pack also contained either one syringe of haloperidol (5 mg/1 ml) plus one syringe of placebo (200 ml) or one syringe of valproate (200 ml) plus one syringe of placebo (1 ml). Two medication packs were assigned to each patient for readministration of medication if the agitation has not been controlled by primary dosing. Upon identification of a potential study candidate by the emergency physician, one pack was selected at random. As a patient underwent randomization, trained physicians, blinded to the pack's contents, completed the patient record and obtained informed consent. Demographic data and related clinical information, such as psychiatric diagnosis, medical comorbidities, level of agitation, and vital signs, were documented. We also included information on previous use of psychiatric medication in the 24 h before starting the study evaluation. After the intervention, the envelope was resealed and attached to a form of the patient's details as a record. A blinded explicit review of the list of treatment assignment and the patient's medical record was performed.

Statistical analysis

The power size of the sample was determined assuming a two-sided significance level of 5% and a power level of 80% ($\beta = 20\%$). We adopted a change of at least one point on the ACES score, considering that these would be meaningful for clinical purposes (SD of 2). Assuming that 10% of patients could not complete the trial, a sample size of 70 patients was required in each group. Data were divided according to whether patients received haloperidol or valproate for agitation. Primary measurement for this study was change in agitation level from baseline to 30 min after the first injection, as measured directly by the ACES score. Secondary measurements for the trial included change in the PANSS-EC and the ABS scores, the effect of medications on vital signs (systemic blood pressure, heart rate, and respiratory rate), the proportion of patients receiving a second dose of study medications, and any drug-induced adverse effect on the patients' clinical state. The differences in preintervention and postintervention vital signs were compared within a single patient and between both study arms. All patients were followed until the end of the trial. According to the trial protocol, all the randomized patients who received at least one of the treatments (intention-to-treat) were evaluated in terms of efficacy and safety analysis. Means (\pm SD) were used to present continuous variables and frequencies (percentages) were computed for categorical variables. Univariate analysis was carried out to test differences in the mean change scores between the treatment groups using an unpaired Student's *t*-test for variables with a normal distribution and the Mann–Whitney *U*-test for variables without a normal distribution. The χ^2 test or Fisher's exact test was used for categorical variables, as appropriate. We considered a two-

sided P value of 0.05 or less to be statistically significant for all tests. Analyses were carried out using SAS statistical software, version 9.3 (SAS Institute, Cary, NC, USA).

Results

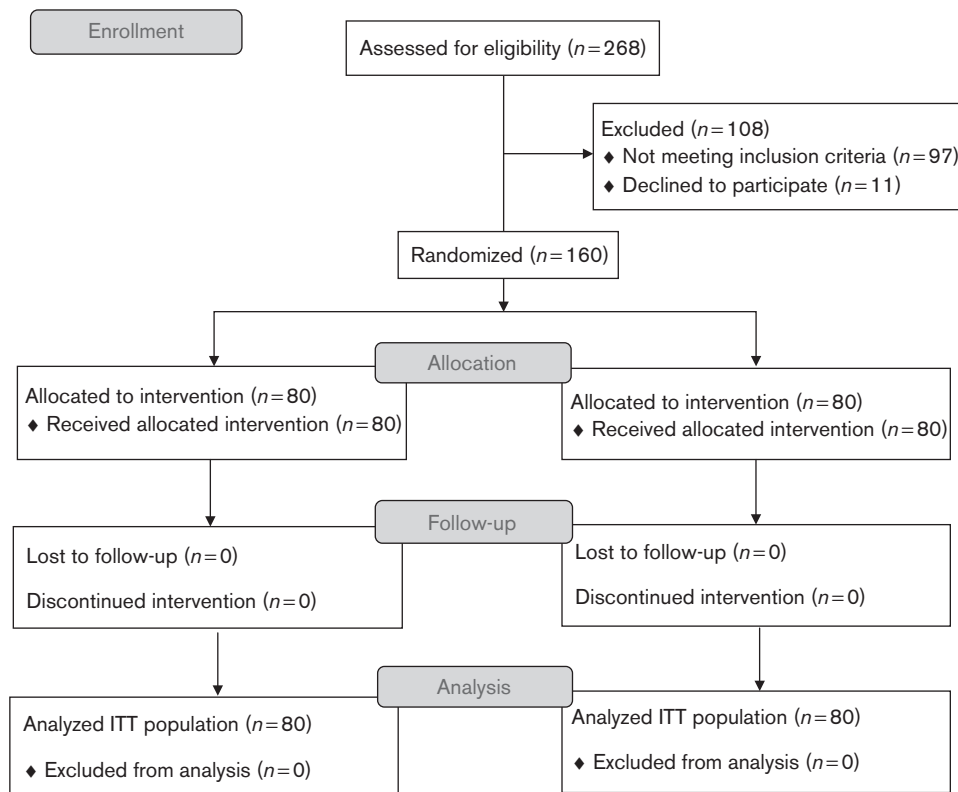
Study population

Between April and July 2014, 268 patients were admitted to the hospital ED. A total of 160 patients fulfilled the inclusion criteria and were entered into the trial (Fig. 1). Ninety-seven patients were excluded for various reasons (n): hypoglycemia (22), head trauma (17), hypotension (systolic blood pressure ≤ 90) (14), breastfeeding (11), history of liver disease (10), history of seizure (10), drug allergy (7), and pregnancy (6). Eleven patients' family members refused consent for participation in the trial. Of the final 160 participants, half of the patients (80 patients) were assigned to receive 5 mg of i.m. haloperidol and 80 were assigned to receive i.v. valproate (20 mg/kg, average dose = 1541.5 ± 286 mg, range 940–2400).

The most common initial clinical diagnoses were psychotic disorders ($n=52$), mood disorders ($n=23$), cognitive impairment ($n=23$), adjustment disorders ($n=17$), others (infection, substance intoxication or withdrawal) ($n=35$), and unknown etiology ($n=10$). Ninety-six

patients were brought to ED by ambulance service and 64 patients reached the hospital by self-transport. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), cognitive impairment was defined as mental disorders affecting cognitive functions, mainly memory processing, perception, and problem solving. The major categories were amnesia, dementia, and delirium. The demographic and clinical features of the two study groups at baseline are shown in Table 1. For the entire study population, the average mean age (\pm SD) was 43.73 ± 7.44 years. At the time of entry into the trial, the patients had a total mean (\pm SD) ACES score of 1.73 ± 0.76 . No statistically significant differences were found with respect to age, sex, severity of agitation, or ED diagnosis between the patients who received haloperidol compared with patients who received valproate. Of all the patients, 124 were on previous psychiatric medication. Of these, 53 were prescribed atypical antipsychotics, 42 were prescribed mood stabilizers, 18 were prescribed antidepressants, and 11 were prescribed others. The previous use of medications did not differ between each arm of the trial (72.5% for haloperidol, 82.5% for valproate, $P=0.130$). The mean (\pm SD) duration of physical restraint (minute) did not differ significantly between patients receiving valproate (37.4 ± 5.5) and haloperidol (38.9 ± 5.8 ,

Fig. 1



The Consolidated Standards of Reporting Trials (CONSORT) patient flow diagram through the trial. ITT, intention-to-treat.

Table 1 Demographic and clinical characteristics of participants by treatment groups (intention-to-treat, n = 160)

Characteristic	Valproate (n = 80)	Haloperidol (n = 80)	P
Age (mean ± SD) (years)	42.95 ± 6.18	44.55 ± 8.80	0.187
Sex (male/female)	53/27	49/31	0.511
Physical restraint [n (%)]	65 (81.2)	61 (76.2)	0.440
Etiology [n (%)]			
Mental disorders ^a	57 (71.2)	55 (68.7)	0.730
Others ^b	17 (21.2)	21 (26.2)	0.457
Unknown	6 (7.5)	4 (5.0)	0.746

^aMental disorders include psychotic disorders, mood disorders, cognitive impairment, and adjustment disorders.

^bOther etiologies include infection, substance intoxication, or withdrawal.

$P=0.100$). The proportion of patients restrained physically was 85.0% (68/80) in the valproate group and 76.2% (61/80) in the haloperidol group, without a statistically significant difference between the drugs ($P=0.161$).

Outcomes

Our analysis showed different clinical effectiveness for treatment with valproate and haloperidol, with a significant change in the baseline ACES score at 30 min. The baseline agitation scores for patients in the valproate group were not significantly different from those in the haloperidol group. Table 2 describes the treatment outcomes in the two trial arms. Before-treatment and after-treatment mean (\pm SD) changes in the ACES score of valproate group did not differ significantly from the haloperidol group (3.08 ± 2.03 vs. 3.62 ± 2.27 , Mann-Whitney U -test, $P=0.072$). The mean score on the ACES at the endpoint was notably larger for valproate-treated patients (4.73 ± 1.93) compared with haloperidol-treated patients (5.45 ± 2.09 , $P=0.028$). At the end of the study, the mean change in the PANSS-EC score from baseline to 30 min after drug injection was -11.74 ($SD=7.18$) for the valproate group and -11.41 ($SD=7.21$) for the haloperidol group ($P=0.649$). At 30 min after the first injection, the mean change in the ABS score for the valproate group was -5.58 ($SD=3.46$) and in the haloperidol group, the mean was -5.89 ($SD=3.31$,

Table 2 Endpoint change in efficacy measures at 30 min after the first injection (intention-to-treat, n = 160)

Characteristics	Valproate (n = 80)	Haloperidol (n = 80)	P
ACES score (means ± SD)			
Baseline	1.64 ± 0.75	1.82 ± 0.76	0.132
Endpoint	4.73 ± 1.93	5.45 ± 2.09	0.028*
PANSS-EC score (means ± SD)			
Baseline	25.38 ± 5.80	24.21 ± 5.59	0.207
Endpoint	12.47 ± 3.47	13.97 ± 6.61	0.080
Difference ^a	-11.74 ± 7.18	-11.41 ± 7.21	0.649
ABS total score (means ± SD)			
Baseline	27.29 ± 4.40	28.28 ± 4.56	0.177
Endpoint	21.70 ± 4.44	22.38 ± 5.14	0.381
Difference ^a	-5.58 ± 3.46	-5.89 ± 3.31	0.651
Second dose ^b [n (%)]	13 (16.2)	17 (21.2)	0.418

ABS, Agitated Behavior Scale; ACES, Agitation-Calmness Evaluation Scale; PANSS-EC, Positive and Negative Syndrome Scale-Excited Component.

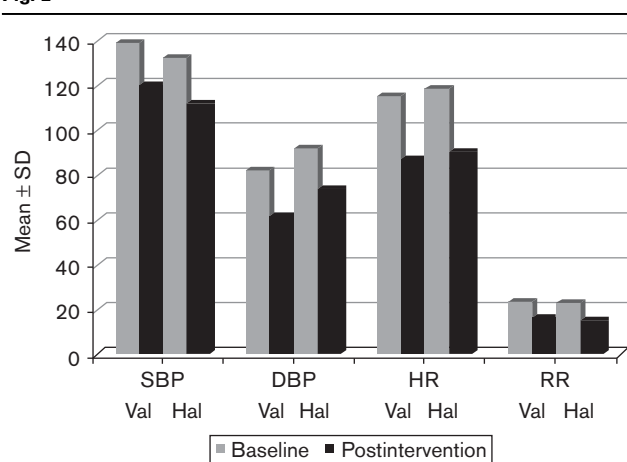
^aThe 30-min minus pretreatment change.

^bUse of an additional dose in patients without agitation improvement after 30 min on the basis of the treating physician's discretion.

$P=0.651$). There was no significant treatment difference in the proportion of patients receiving a second injection after the 30 min period ($P=0.341$). All patients with an episode of agitation recovered. The patients were ambulatory at the time of discharge from the emergency service or upon transfer to a psychiatric department.

Adverse events

There were no acute allergic reactions to either medication. There were no statistically significant differences up to 30 min after injection with respect to changes in systolic and diastolic blood pressure ($P=0.77$, $P=0.12$), heart rate ($P=0.64$), and respiratory rate ($P=0.78$) among patients receiving each of the interventions. Thus, there were no significant advantages to either haloperidol or valproate with respect to change in vital signs (Fig. 2). There was an overall significant difference ($P=0.019$) among treatment groups in the proportion of patients who experienced at least one drug-induced AE. The haloperidol treatment group had a significantly larger proportion of patients who showed at least one AE (37/80, 46.2%) than the valproate treatment group (24/80, 30.0%, $P=0.034$). Intense sedation 30 min after intervention was the most frequent AE that occurred, with an incidence of 36.2% (29/80, $P<0.001$) in the haloperidol treatment group and 2.5% (2/80) in the valproate treatment group. Participants were considered to be sedated if, on observation, they appeared to be asleep with depression of consciousness and were not aroused by voice stimulation (American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002). Vomiting and headache occurred, with an incidence of 16.2% (13/80, $P<0.001$) and 11.2% (9/80, $P=0.002$) in the

Fig. 2

Vital signs of preintervention and postintervention by treatment groups. No significant changes in systemic blood pressure, heart rate, and respiratory rate were found for the intergroup comparison and comparison between two groups (all $P>0.05$). DBP, diastolic blood pressure; Hal, haloperidol; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; Val, valproate.

valproate treatment group, compared with no patients in the haloperidol group. Moreover, seven patients (8.7%, $P=0.007$) experienced EPS in the haloperidol study arm than no patients in the valproate arm. These patients received anticholinergic agents. Hypotension occurred in one patient receiving haloperidol.

Discussion

Pharmacological management of acute agitation in an emergency setting should include an ideal medication with a fast onset of action; modest interpatient variability in pharmacodynamics and pharmacokinetics; and low risk for AEs and tranquilization without intense sedation, which may interfere with physical evaluation, diagnosis, and selection of further therapy (Allen *et al.*, 2003; Zimbroff, 2003). The American College of Emergency Physicians guidelines for the pharmacologic management of agitated patients in ED include usage of a benzodiazepine or a typical antipsychotic (haloperidol) as a primary monotherapy (Lukens *et al.*, 2006). However, despite the rapid effect of parenteral classic antipsychotics for calming agitated patients, a wide spectrum of adverse effects restricts their usage. Major drawbacks include extreme sedation, orthostatic hypotension, EPSs (dystonia, akathisia, and parkinsonism), and the risk of neuroleptic malignant syndrome (Salzman *et al.*, 1991). An open-label study on single-dose oral haloperidol (5 mg) in healthy adult volunteers found that dysphoria occurred in ~40% of patients (Breier *et al.*, 2002). In a 24-h randomized trial of 270 patients with psychotic disorders Breier *et al.* (2002), reported that haloperidol was associated with parkinsonism (16.7%) and akathisia (7.9%). Tran-Johnson *et al.* (2007) came to a similar conclusion in a study that compared aripiprazole with haloperidol and placebo. Haloperidol led to overall side effects of sedation (12.3%), akathisia (10.5%), dizziness (7.0%), and dystonia (7.0%). Moreover, sedation and autonomic effects are frequently observed in patients receiving either i.m. or oral haloperidol (Yildiz *et al.*, 2003). In the current study, patients experienced a deep sedative effect after the administration of the haloperidol drug that appeared to be interfering with clinical evaluation and diagnosis. In addition, we found that EPSs with haloperidol monotherapy occurred at a rate of 9.3%, corresponding with the rate estimated in previous studies, ranging from 5 to 21% (King *et al.*, 1995; Meehan *et al.*, 2001; Breier *et al.*, 2002; Yildiz *et al.*, 2003; Huf *et al.*, 2007; Tran-Johnson *et al.*, 2007). The noticeable increase in the use of valproate since 1994 does not seem to be because of its FDA approval for manic episodes associated with bipolar disorder. It may be attributable to the perceived effectiveness of valproate for other conditions. Agitation and aggressive behavior is a complex phenomenon associated with genetic, psychosocial, and neurobiological factors; impairments of many neurotransmitter systems including monoamines, glutamate, and γ -aminobutyric acid are implicated in the biology of this condition (Nelson and Chiavegatto, 2001; Gobbi and Debonnel, 2003). Recently, antiepileptic drugs, such

as valproic acid, have been receiving considerable attention for its potential role in the control of aggression and agitation (Lindenmayer and Kotsaftis, 2000; Hollander *et al.*, 2003, 2005). Furthermore, it is believed to reduce impulsive behavior, which is useful for some patients with schizophrenia (Citrome *et al.*, 2000, 2004; Citrome, 2003). Randomized-controlled trials with valproate semisodium have also been conducted to evaluate its effects on behavioral symptoms in elderly dementia populations (Porsteinsson *et al.*, 2001; Sival *et al.*, 2002; Tariot *et al.*, 2005). Although our data do not focus on these patients specifically, we speculate that the perception that valproate is useful in controlling irritability, hostility, and aggressivity is the driving force behind its popularity. To date, no studies for comparison of valproate as a sole treatment versus antipsychotic drugs for aggressive behavior because of several etiologies have been found. In the present study, we confirmed that valproate provided effective and well-tolerated sedation for agitated patients in an ED setting. At 30 min after the first injection, the valproate treatment group improved similarly to the haloperidol treatment group on the PANSS-EC and ABS measures of agitation, whereas valproate was significantly better than haloperidol for the ACES score. This result was because of the larger proportion of patients who experienced intense sedation in the haloperidol group, as measured by ACES.

The neurobiological mechanism by which valproate exerts its therapeutic effect in agitated behaviors of neuropsychiatric disorders is not well understood. Several hypotheses have been proposed on the scope and mechanism of action. The potential mechanisms involve imitating the effects of the inhibitory neurotransmitter (γ -aminobutyric acid) (Salloum *et al.*, 2005), inhibiting the corticotrophin-releasing factor (Post *et al.*, 1992), and increasing 5-hydroxy-indoleacetic acid in cerebrospinal fluid to stimulate the serotonergic system (Gobbi *et al.*, 2006), all of which may conceivably play a role in agitated behaviors. The management of agitated patients in an emergency setting could be facilitated by the development of an easy-to-administer medication. Even though i.v. treatment with an anticonvulsant agent is an effective sedative for adult, it has some disadvantages. There is a concern that application of injective drugs may compromise the physician-patient relationship. i.v. or i.m. administration of medications to an agitated patient has also been correlated with the risk for needlestick injuries to ED staff (Fisman *et al.*, 2003). Also, inserting an i.v. line may be difficult and potentially dangerous in an agitated patient (Huf *et al.*, 2002). Consequently, parenteral treatment should be applied cautiously for patients who cannot cooperate with the physician for oral treatment and need rapid management or benefit from parenteral intervention. It should be noted that i.m. use of psychopharmacological medications may be less invasive and causes no failed peripheral i.v. access compared with i.v. treatments that would require the arms to be

restrained physically. Further, on the basis of patients' right principals and safety protection, i.v. drugs are intrusive when i.m. medications are available. Besides the advantages of i.m. administered antipsychotics, this route led to slower peak plasma concentration with a delayed onset of action compared with i.v. treatment (Ayd, 1978).

In the present trial, we preferred to administer haloperidol i.m., which appeared to be effective for rapid tranquilization with fewer cardiotoxic effects compared with i.v. route of administration. It is well established that haloperidol may prolong the QT interval by blocking the repolarizing potassium current (Douglas and Block, 2000). Prolongation of the QT interval has been associated with subsequent malignant cardiac arrhythmias including ventricular fibrillation and torsades de pointes (Tisdale *et al.*, 2007). Acutely behaviorally disturbed patients may be at particular risk if QT prolongation occurs as adrenalin may sensitize the heart, making arrhythmias more likely (Royal College of Psychiatrists Psychopharmacology Sub-Group, 1997; Haverkamp *et al.*, 2000). These cardiac side effects were increased with i.v. administration of haloperidol (Meyer-Masseti *et al.*, 2010). Given these concerns, clinical caution is advised on the use of parenteral haloperidol (McAllister-Williams and Ferrier, 2002).

Patients frequently present to the ED with different forms of acute distress situations. Because of the nature of emergency medicine and the varied patient populations, it is not always possible to obtain informed consent from the patients. To carry out a research, investigators must make every reasonable effort to ensure the safe participation of patients in the study, protect their rights, and involve the patients and/or their family in the consent process. Despite the safeguards imposed by institutional review boards and the consent process, prospective researchers may still have problems with ethical considerations. Therefore, the individual patients' rights and welfare must be observed and guarded strictly; they should be provided with necessary information about the study to decide whether they wished to continue to participate and they should be provided the opportunity to refuse further experimental treatment (Spivey *et al.*, 1991; Erler and Thompson, 2008). In the present study, for the patients without decision-making capacity, that is, those who were not mentally capable of understanding the situation and consenting, their family members, relative, or legal guardian signed a written consent and were fully informed about the risks and benefits of i.v./i.m. use of the medications. Then, the treatment was explained to the patients when they were capable of understanding the study interventions. The population of this trial is representative of patients observed in a psychiatric emergency setting because it includes patients who were agitated because of several potential causes, such as schizophrenia, schizoaffective

disorder, cognitive impairment, delusional disorder, and mood disorder, with the exclusion of those who were not able to take medications because of hypersensitivity or hepatic failure. Therefore, the results of this study are applicable to general EDs and inpatients in psychiatric setting. According to the present trial, i.v. valproate can be useful as an efficacious method for the management of agitation in a clinical setting of emergency psychiatry because of its broad therapeutic spectrum, relatively benign side-effect profile, and rapid onset of action (Vance *et al.*, 2003). Of note, it provided a satisfactory level of sedation compared with a huge proportion of patients with intense sedation in the haloperidol group. Therefore, this advantage could potentially allow the emergency physicians to obtain a proper clinical history and determine the underlying diagnosis before making any additional treatment decisions.

Limitations

There are several limitations to this trial. First, there was no placebo control group. A separate placebo group would have been principally useful in documenting efficacy and comparing agitation scores and changes in vital signs. However, we believe that it was ethically and practically impossible to use a placebo because most of our study participants required urgent intervention. Second, a limitation of this study could be the assessor-blinded evaluation of outcomes as the use of different sites of drug administration might lead to difficulty in ensuring assessor blindness. In addition, the difference between the treatment groups with respect to the type of administration might result in bias in favor of the i.v. valproate treatment because of the potential delay of action of i.m. administration. Third, the lack of follow-up information limits our ability to arrive at more conclusions. Follow-up at least 48 h after ED discharge, to record agitation recurrence, further drug-induced AEs, and return to another medical facility would be beneficial. However, review of the medical documents of the patients in this study showed no ED revisits within a 48-h window. This review was not inclusive for follow-up visits to other medical facilities or private physician offices. Fourth, we did not compare the efficacy and safety of study medications during several temporal endpoints. Therefore, future study to examine the effectiveness of different treatment dosing at different time intervals is warranted.

Conclusion

To the best of our knowledge, this is the first randomized, double-blind clinical study comparing the use of valproate versus haloperidol for tranquilization of acutely agitated patients in the ED. Our results suggest that valproate therapy may be useful in patients with agitation. However, side effects such as headache, vomiting, and teratogenicity may limit its application. In our investigation, the incidence of vomiting was more

frequent in the valproate arm compared with the haloperidol arm, which is considered unsafe with respect to the risk of aspiration in acutely agitated patients. Moreover, exposure to valproate during pregnancy is potentially harmful to a fetus (Holmes et al., 2001). Therefore, teratogenicity and other adverse developmental effects are major concerns and specific caution is warranted in the use of valproate during pregnancy (NHS, 2004).

In addition to these limitations in valproate therapy, the i. v. route of the drug administration needs some form of vascular access, which is difficult to establish for severely agitated patients, and physical restraint is required. However, the injectable form of the drug cannot be administered i.m.

In summary, this trial has highlighted the need for future comprehensive risk/benefit analyses to evaluate the efficacy of mood stabilizers in the management of acute agitation and recommend which medication is best under a given circumstance. As more information become available on the use of mood-stabilizing drugs compared with classic antipsychotics in emergency situations, additional refinement of the treatment of agitation and the development of specific algorithms will be practicable.

Acknowledgements

The authors gratefully acknowledge the patients, families, and staff who made this study possible.

Conflicts of interest

There are no conflicts of interest.

References

- Allen MH (2000). Managing the agitated psychotic patient: a reappraisal of the evidence. *J Clin Psychiatry Suppl* 14:11–20.
- Allen MH, Carpenter D, Sheets JL, Miccio S, Ross R (2003). What do consumers say they want and need during a psychiatric emergency? *J Psychiatr Pract* 9:39–58.
- American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists (2002). Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology* 96:1004–1017.
- Ayd Jr, Frank J (1978). Intravenous haloperidol therapy. *Psychopharm Rev* 13:20–23.
- Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L, et al. (1997). Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med* 15:335–340.
- Breier A, Meehan K, Birkett M, David S, Ferchland I, Sutton V, et al. (2002). A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Arch Gen Psychiatry* 59:441–448.
- Cañas F (2007). Management of agitation in the acute psychotic patient—efficacy without excessive sedation. *Eur Neuropsychopharmacol Suppl* 2: S108–S114.
- Citrome L (2003). Schizophrenia and valproate. *Psychopharmacol Bull Suppl* 2:74–88.
- Citrome L, Levine J, Allingham B (2000). Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatr Serv* 51:634–638.
- Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA (2004). Effects of adjunctive valproate on hostility in patients with schizophrenia receiving olanzapine or risperidone: a double-blind multi-center study. *Psychiatr Serv* 55:290–294.
- Dolder C, McKinsey J (2010). Low-dose divalproex in agitated patients with Alzheimer's disease. *J Psychiatr Pract* 16:63–67.
- Douglas PH, Block PC (2000). Corrected QT interval prolongation associated with intravenous haloperidol in acute coronary syndromes. *Catheter Cardiovasc Interv* 50:352–355.
- Dubin WR, Feld JA (1989). Rapid tranquilization of the violent patient. *Am J Emerg Med* 7:313–320.
- Eli Lilly (2004). Comparisons of intramuscular olanzapine and intramuscular haloperidol in patients with schizophrenia. Eli Lilly and Co Clinical Trial. Clinical Trials. Gov identifier NCT00088478.
- Erler CJ, Thompson CB (2008). Part II: ethics, human rights, and clinical research. *Air Med J* 27:110–113.
- Fisman DN, Harris AD, Sorock GS, Mittleman MA (2003). Sharps-related injuries in health care workers: a case-crossover study. *Am J Med* 114:688–694.
- Gobbi G, Debonnel G (2003). What is a recommended treatment for aggression in a patient with schizophrenia? *J Psychiatry Neurosci* 28:320.
- Gobbi G, Gaudreau PO, Leblanc N (2006). Efficacy of topiramate, valproate, and their combination on aggression/agitation behavior in patients with psychosis. *J Clin Psychopharmacol* 26:467–473.
- Grunze H, Erfurth A, Amann B, Giupponi G, Kammerer C, Walden J (1999). Intravenous valproate loading in acutely manic and depressed bipolar I patients. *J Clin Psychopharmacol* 19:303–309.
- Haverkamp W, Breithardt G, Camm AJ, Janse MJ, Rosen MR, Antzelevitch C, et al. (2000). The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc Res* 47:219–233.
- Hilty DM, Rodriguez GD, Hales RE (1998). Intravenous valproate for rapid stabilization of agitation in neuropsychiatric disorders. *J Neuropsychiatry Clin Neurosci* 10:365–366.
- Hollander E, Tracy KA, Swann AC, Coccaro EF, McElroy SL, Wozniak P, et al. (2003). Divalproex in the treatment of impulsive aggression: efficacy in cluster B personality disorders. *Neuropsychopharmacology* 28:1186–1197.
- Hollander E, Swann AC, Coccaro EF, Jiang P, Smith TB (2005). Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry* 162:621–624.
- Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM (2001). The teratogenicity of anticonvulsant drugs. *N Engl J Med* 344:1132–1138.
- Huf G, Coutinho ES, Adams CE. TREC-Rio trial (2002). TREC-Rio trial: a randomized controlled trial for rapid tranquillisation for agitated patients in emergency psychiatric rooms [ISRCTN44153243]. *BMC Psychiatry* 2:11.
- Huf G, Coutinho ES, Adams CE. TREC Collaborative Group (2007). Rapid tranquillisation in psychiatric emergency settings in Brazil: pragmatic randomized controlled trial of intramuscular haloperidol versus intramuscular haloperidol plus promethazine. *BMJ* 335:869.
- Janssen PA, Niemegeers CJ, Schellekens KH, Verbruggen FJ, Van Nueten JM (1963). The pharmacology of dehydrobenzperidol, a new potent and short acting neuroleptic agent chemically related to Haloperidol. *Arzneimittelforschung* 13:205–211.
- Kay SR, Fiszbein A, Opler LA (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 13:261–276.
- King DJ, Burke M, Lucas RA (1995). Antipsychotic drug-induced dysphoria. *Br J Psychiatry* 167:480–482.
- Kunen S, Niederhauser R, Smith PO, Morris JA, Marx BD (2005). Race disparities in psychiatric rates in emergency departments. *J Consult Clin Psychol* 73:116–126.
- Lindenmayer JP (2000). The pathophysiology of agitation. *J Clin Psychiatry Suppl* 14:5–10.
- Lindenmayer JP, Kotsaftis A (2000). Use of sodium valproate in violent and aggressive behaviors: a critical review. *J Clin Psychiatry* 61:123–128.
- Lonerger ET, Cameron M, Luxenberg J (2004). Valproic acid for agitation in dementia. *Cochrane Database Syst Rev* 2:CD003945.
- Lukens TW, Wolf SJ, Edlow JA, Shahabuddin S, Allen MH, Currier GW, Jagoda AS. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department (2006). Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med* 47:79–99.
- McAllister-Williams RH, Ferrier IN (2002). Rapid tranquillisation: time for a reappraisal of options for parenteral therapy. *Br J Psychiatry* 180:485–489.
- Meehan K, Zhang F, David S, Tohen M, Janicak P, Small J, et al. (2001). A double-blind, randomized comparison of the efficacy and safety of intramuscular

- injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J Clin Psychopharmacol* **21**:389–397.
- Meyer-Massetti C, Cheng CM, Sharpe BA, Meier CR, Guglielmo BJ (2010). The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *J Hosp Med* **5**:E8–E16.
- National Collaborating Centre for Nursing and Supportive Care (UK) (2005). *Violence: the short-term management of disturbed/violent behaviour in in-patient psychiatric settings and emergency departments*. London: Royal College of Nursing (UK).
- Nelson RJ, Chiavegatto S (2001). Molecular basis of aggression. *Trends Neurosci* **24**:713–719.
- NHS (2004). *Newer drugs for epilepsy in adults*. London: National Institute for Clinical Excellence (NICE). NICE Technology Appraisal 76. <http://www.nice.org.uk/guidance/ta76>. [Accessed 3 December 2014].
- Porsteinsson AP, Tariot PN, Erb R, Cox C, Smith E, Jakimovich L, et al. (2001). Placebo-controlled study of divalproex sodium for agitation in dementia. *Am J Geriatr Psychiatry* **9**:58–66.
- Post RM, Weiss SR, Chuang DM (1992). Mechanisms of action of anticonvulsants in affective disorders: comparisons with lithium. *J Clin Psychopharmacol* **12** (Suppl):23S–35S.
- Pratt P, Chandler-Oatts J, Nelstrop L, Branford D, Periera S, Johnston S (2008). Establishing gold standard approaches to rapid tranquillisation: review and discussion of the evidence of the safety and efficacy of medications used. *J Psychiatr Intensive Care* **4**:43–57.
- Royal College of Psychiatrists Psychopharmacology Sub-Group (1997). *The association between antipsychotic drugs and sudden death. Council Report CR57*. London: Royal College of Psychiatrists.
- Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME (2005). Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry* **62**:37–45.
- Salzman C, Solomon D, Miyawaki E, Glassman R, Rood L, Flowers E, Thayer S (1991). Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry* **52**:177–180.
- Sival RC, Haffmans PM, Jansen PA, Duursma SA, Eikelenboom P (2002). Sodium valproate in the treatment of aggressive behavior in patients with dementia – a randomized placebo controlled clinical trial. *Int J Geriatr Psychiatry* **17**:579–585.
- Spivey WH, Abramson NS, Iserson KV, MacKay CR, Cohen MP (1991). Informed consent for biomedical research in acute care medicine. *Ann Emerg Med* **20**:1251–1265.
- Tariot PN, Raman R, Jakimovich L, Schneider L, Porsteinsson A, Thomas R, et al. (2005). Divalproex sodium in nursing home residents with possible or probable Alzheimer disease complicated by agitation: a randomized, controlled trial. *Am J Geriatr Psychiatry* **13**:942–949.
- Tesar GE (1993). The agitated patient, Part I: evaluation and behavioral management. *Hosp Community Psychiatry* **44**:329–331.
- Thomas H Jr, Schwartz E, Petrilli R (1992). Droperidol versus haloperidol for chemical restraint of agitated and combative patients. *Ann Emerg Med* **21**:407–413.
- Tisdale JE, Kovacs R, Mi D, McCabe GP, Cariera BL, Sharma N, Rosman H (2007). Accuracy of uncorrected versus corrected QT interval for prediction of torsade de pointes associated with intravenous haloperidol. *Pharmacotherapy* **27**:175–182.
- Tran-Johnson TK, Sack DA, Marcus RN, Auby P, McQuade RD, Oren DA (2007). Efficacy and safety of intramuscular aripiprazole in patients with acute agitation: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* **68**:111–119.
- Vance H, Kauffman C, Miller B, Mansour T (2003). Treatment of agitation using Depakote: a patient with dementia. *Psychiatry* **66**:358–359.
- Yildiz A, Sachs GS, Turgay A (2003). Pharmacological management of agitation in emergency settings. *Emerg Med J* **20**:339–346.
- Zimbroff DL (2003). Management of acute psychosis: from emergency to stabilization. *CNS Spectr* **8** (Suppl 2):10–15.
- Zun LS, Downey LV (2008). Level of agitation of psychiatric patients presenting to an emergency department. *Prim Care Companion J Clin Psychiatry* **10**:108–113.