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Sodium Valproate versus Continuous Infusion of Haloperidol in Management of Agitated Critically Ill Patients

Ramadan Khalil*, Mohamed Soliman, Mohamed Omer, Kamel Abdel Aziz, Khaled Hussein

Cairo University, Cairo, Egypt

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***Correspondence:** Ramadan Khalil. Cairo University, Cairo, Egypt.. E-mail: ramadan_200881@yahoo.com

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Abstract

AIM: Describe the efficacy and safety of valproate and haloperidol infusion in controlling agitation in the intensive care unit (ICU).

MATERIAL AND METHODS: Prospective study on 100 critically ill patients with agitation in Kasralainy Hospital over the period from May 2016 to June 2017.patients were divided into two groups, each group included 50 patients, 1st group patients received Depakene orally, and 2nd group patients received haloperidol by i.v infusion for 72 h. Richmond agitation sedation score and doses of additional sedative drugs were noted and calculated daily in the first three days.

RESULTS: Our study showed that valproate was equal in efficacy in controlling agitation; decreasing the RAAS significantly after 48 h from initiation (2.52 ± 0.61 vs 0.28 ± 0.54 with $p < 0.001$) for Depakene and (2.6 ± 0.67 vs 0.34 ± 0.48 with $p < 0.001$) for haloperidol. There was also a decrease in the doses of additional sedative drugs used to control agitation (midazolam & propofol) after 48 h from drug initiation. Both drugs therapy was associated with decrease in heart rate (89 ± 20 vs 86.6 ± 13.6 with $p = 0.002$ for valproate and 99.8 ± 23.3 vs 91 ± 16.7 with $p < 0.001$ for haloperidol). They did not affect blood pressure. Haloperidol therapy was associated with significant QTc prolongation.

CONCLUSION: Valproate was equal in efficacy as haloperidol infusion in controlling agitation in ICU and decreasing the doses of additional sedative drugs used after 48 h from initiation.

Introduction

Agitation occurs in up to 70% of critically ill patients and is a significant source of distress for patients, families, and providers (Fraser GL et al., 2000). Sedatives are administered to 50% of intensive care unit (ICU) patients to alleviate agitation [1]. Choice of sedative is complex and largely driven by patient context. No sedative has consistently been shown to be superior to the rest, and alternative agents are greatly needed [2]. Most ICU patients, especially those requiring mechanical ventilation, are treated with opioids, propofol, and/or benzodiazepines [1], [3]. Use of these agents is limited by adverse effects (e.g., hemodynamic derangement) for safe administration [4]. New therapies for treating agitation are rarely introduced into practice, with dexmedetomidine being the most recent in 1999. Consequently, providers have increasingly repurposed older pharmacologic agents as ICU sedatives (e.g., clonidine, Phenobarbital, and valproate (Depakene) [5], [6].

Haloperidol is a butyrophenone that works by blocking D2 receptors, probably in the mesolimbic region [7]. Its side effects include extrapyramidal symptoms, and rarely, the neuroleptic malignant syndrome [8]. The patient should be monitored for precipitation of arrhythmias such as torsade de points [9] and haloperidol should be used with caution in patients with a QTc interval of over 450 msec. National guidelines for the management of agitation/delirium recommend short term haloperidol if non-pharmacological measures are not effective.

Depakene is an antiepileptic and mood stabiliser approved for the treatment of seizures, manic episodes associated with bipolar disorder, and migraine prophylaxis. Mechanistically, it blocks voltage-dependent sodium and calcium channels, increases γ-aminobutyric acid (GABA) synthesis, potentiates GABA activity at postsynaptic receptors, blocks GABA degradation, and attenuates the activity of glutamate upon N-methyl-D-Aspartate receptors

[10], [11].

Recently, valproate has been administered to critically ill patients to treat agitation and delirium, but there are few published reports to support this practice [12], [13], [14]. Valproate is an emerging treatment for ICU agitation because it allows patients to interact with their caregivers; can be administered outside of the ICU; has both an intravenous (IV) and enteral formulation; has a low drug acquisition cost; and has not been associated with respiratory depression, hemodynamic derangements, or delirium. In this study, we describe the use of Depakene & haloperidol for agitation in critically ill patients and examine their safety.

We aimed to evaluate the adding effect of a calcium sensitiser (levosimendan) compared to the conventional inotropic and vasoactive agent used in the patient with poor left ventricular function undergoing cardiac surgery on different measured hemodynamic variables and the effect on the outcome.

Material and Methods

Study design

Our study was a prospective one on Agitated critically ill patients in kasralainy hospital, critical care department over the period from May 2016 to June 2017. Patients included if they were above 18 years old and has severe agitation (score ≥ 2 on RAAS) patients were excluded if they have advanced cardiac diseases, hepatic diseases, advanced malignancy or if they were on antiepileptic. Our study was conducted on 100 patients divided in two groups; each group included 50 patients. Patients in group I received Depakene orally, and patients in group II received haloperidol by i.v. Infusion for 72 h.

Demographic data and patients' characteristics

Patient demographic data included age, sex, weight, history of psychiatric diagnosis, alcohol or substance abuse, the reason for ICU admission, need for mechanical ventilation. Clinical outcomes were descriptive and included ICU length of stay and ICU mortality.

Efficacy outcomes

Efficacy data were collected from day of drug (valproate or haloperidol) initiation and continuing for 72 h or until discontinuation, whichever came first. The 3-day interval was selected to allow a reasonable time to observe efficacy or lack thereof, the agitated patients were examined daily and Richmond Agitation-Sedation Scale (RASS) was assessed daily from drug initiation up to 3days. Also, the doses of additional sedative drugs were noted and documented daily during drug therapy.

Safety outcomes

Safety parameters were examined for the hospital duration of valproate and haloperidol therapy. Records were specifically reviewed for possible hepatotoxicity, hematologic toxicity for both drugs and QTc prolongation for haloperidol. The number of patients who had discontinued because of a suspected adverse event was also recorded. Hepatotoxicity was defined as a new alanine aminotransferase 3 times the upper limit of normal (120 U/L), alkaline phosphatase 2 times the ULN (234 U/L), total bilirubin 2 times the ULN (2 mg/dL), or a doubling of the baseline value if it was already abnormal following drug initiation. Suspected cases of hepatotoxicity were further assessed using the validated Roussel Uclaf Causality Assessment Method (RUCAM) [15]. Hematologic toxicity was defined as a new leukocyte count 4200 cells/mm3, absolute neutrophil count 2400 cells/mm3, or platelet count 140 000 cells/mm3 or platelet drop by 50% if platelets were already 140 000 cells/mm3 following valproate initiation.

Results

Demographic data and patient characteristics

One hundred patients were included in the study. The mean age of the studied population was 63.7 ± 15 years; the youngest was 22 years; they included 54 Males and 46 Females. Regarding Comorbidities; in our study 36 Smokers, 42 with pre-existing Cardiac patients (Ischemic heart disease and chronic heart failure) and 39 with pre-existing Renal patients (serum creatinine ≥ 1.4 mg/dl). End organ failure (45%), sepsis (40%) and Stroke (hemorrhagic and non-hemorrhagic) (15%) were the most common reasons for ICU admissions. The mean length of ICU stay was 7 days, 21 patients died in the ICU.

Table 1: Baseline characteristic data of the total population

Age (mean ± SD) years	63 ± 15
Gender-females n	46
Weight (mean ± SD) kg	76.5 ± 14
Smokers n (%)	36
Pre exciting Cardiac disease n (%)	42
Pre exciting Renal disease n (%)	39
ICU Mortality (%)	21%
ICU stay (mean) days	7
Causes of admission	
End Organ failure (%)	45%
Sepsis (%)	40%
Stroke (%)	15%

Efficacy outcomes

Regarding valproate group; the severity of agitation decreased after 48 h from starting valproate therapy; RASS score decrease from 2.52 ± 0.61 to 0.28 ± 0.54 before and after depakene initiation respectively with P value < 0.001. The doses of concomitant sedative drugs used to control agitation (midazolam & propofol) decreased after 48h from drug initiation (77.2 ± 82.4 mg/day vs. 0 mg/day) and (3.5 ± 2.0 gm/day vs. 0.35 ± 0.49 gm/day) with P value 0.004 and 0.135 respectively. Regarding haloperidol group; the severity of agitation decreased after 48 h from starting valproate therapy; RASS score decrease from 2.6 ± 0.67 Vs 0.34 ± 0.48 before and after depakene initiation respectively with P value < 0.001. The doses of concomitant sedative drugs used to control agitation (midazolam & propofol) decreased after 48 h from drug initiation (101 ± 141 mg/day vs. 16 ± 33 mg/day) and (1.6 ± 1.9 gm/day vs. 0.33 ± 0.7 gm/day) with P value < 0.001.

Hemodynamic response

The Depakene group showed a statistically significant difference regarding HR after 48 h from valproate therapy (89 ± 20 vs 86.6 ± 13.6) with P-value 0.002, there was no effect on systolic or diastolic blood pressure. Haloperidol group showed a statistically significant difference regarding HR after 48 h from haloperidol (99.8 ± 23.3 vs 91 ± 16.7) with P-value < 0.001, there was no effect on systolic or diastolic blood pressure.

Table 2: Efficacy outcomes and hemodynamic response for both groups

	Depakene group		Haloperidol group	
	Day 0	Day 2	Day 0	Day 2
RASS	2.52 ± 0.61	0.28 ± 0.54	2.6 ± 0.67	0.34 ± 0.48
Midazolam	0.77 ± 0.82	0	101 ± 141	16 ± 33
Propofol	3.5 ± 2.0	0.35 ± 0.49	1.6 ± 1.2	0.33 ± 0.7
Heart rate	89 ± 20	86 ± 13	99.8 ± 23	91 ± 16.7
Systolic BP	125 ± 18.8	121.8 ± 10	124.8 ± 17.7	122.6 ± 11.7
Diastolic BP	79.4 ± 8.6	78 ± 5.6	80.6 ± 6	80.4 ± 5

Safety outcomes

All patients had complete blood picture & liver function tests monitored during drug therapy, In valproate group; Hemoglobin level and Total leucocytic count showed significant decrease after 48 h from valproate therapy with p = 0.002 & 0.025 respectively. Liver enzymes (ALT & AST) showed a significant increase after 48 h from valproate therapy with p < 0.0001. One patient developed hepatotoxicity (elevation of ALT ≥ 120 IU/ml) but was unrelated to the drug as his RUCAM score was 1. Regarding haloperidol group; Hemoglobin level & Total leucocytic count showed significant decrease after 48 h from haloperidol therapy with p = 0.004 & < 0.001 respectively. Liver enzymes (ALT & AST) showed no significant differences after 48 h from haloperidol therapy. One patient developed hepatotoxicity (elevation of ALT ≥ 120 IU/ml) but was unrelated to the drug as his RUCAM score was 3. There was significant QTc prolongation after 48 h from haloperidol initiation with p < 0.001, but this was not associated with major cardiac events (VT or VF).

Table 3: Safety outcomes and hemodynamic response for both groups

	Depakene group		Haloperidol group	
Lab	Day 0	Day 2	Day 0	Day 2
Hemoglobin gm/dl	10.6 ± 1.9	10.2 ± 1.5	10.6 ± 1.9	10 ± 1.7
Total leucocytic count cells x 10^3	10.7 ± 9	9.2 ± 7	13 ± 8	10 ± 5
Platelets cells x 10^3	253 ± 103	245 ± 102	209 ± 88	212 ± 94
ALT IU/ml	44 ± 32	49 ± 100	49 ± 83	39 ± 36
AST IU/ml	39 ± 25	48 ± 126	47 ± 66	39 ± 33
Bilirubin IU/ml	0.62 ± 0.5	0.58 ± 0.47	1.32 ± 2.5	1.2 ± 2.3

Discussion

Regarding efficacy outcomes in Depakene & haloperidol groups of our study, there was a significant decrease in the severity of agitation after 48 h from drug initiation with Richmond agitation sedation scores p < 0.001. Also, there was a marked decrease in the doses of concomitant sedative drugs used to control agitation (Midazolam & propofol) after 48 h from drug initiation. Similarly, *Gagnon et al., (2017)* performed a retrospective cohort study evaluated critically ill adults treated with Depakene for agitation on Fifty-three patients and showed that the incidence of agitation significantly decreased following the initiation of Depakene from 96% to 61% on Depakene day 3 (P < 0.001). Also, in this study, Depakene therapy was associated with reduced doses of concomitant sedative drugs [16]. *Riker et al. (1994)* evaluated the Continuous infusion of haloperidol in critically ill agitated patients. This study was performed on eight patients required mechanical ventilation who had severe agitation which was refractory to intermittent bolus treatment with benzodiazepines, narcotics, and haloperidol. These patients received Continuous infusion of haloperidol to maintain adequate sedation. This study showed that there was a significant decrease in the Sedation-Agitation Scale after 48 h from haloperidol initiation (+2.4 vs +0.8) and (P = 0.06). Also, there was a marked reduction in the daily total of non-haloperidol sedatives after 48h of continuous infusion of haloperidol with (P-value = 0.15) [17].

Regarding Hemodynamics response after Depakene & haloperidol initiation, our study showed that there was significant decrease in patients heart rate after 48 h from drug initiation with p = 0.002 & < 0.001 respectively, blood pressure showed no significant changes before and after drug initiation. *Sinha et al., (2000)* reviewed hospital records of 13 patients with status epileptics and hypotension who received IV Depakene therapy. There were no significant changes in blood pressure, pulse, or use of vasopressors. The data suggest that Depakene

loading is well tolerated, even in patients with cardiovascular instability [18], also *Riker, et al., (1994)* evaluated the Continuous infusion of haloperidol in eight critically ill agitated patients. There were no hypotension episodes noted [17].

Regarding safety outcomes, our study showed that hepatotoxicity (ALT ≥ 120 IU/ml) had developed for one patient (2%) hepatotoxicity is unlikely to be related to the drug (Depakene or haloperidol) as RUCAM score was 1 and 3 respectively which make hepatotoxicity is unlikely related haloperidol [15]. Possible reasons for hepatotoxicity in these patients are the underlying disease.

QTc prolongation for all patients in the haloperidol group with one patient had significant QTc prolongation ≥ 500msec after 48 h from haloperidol therapy, but this QTc prolongation was not associated with major cardiac events. That agrees with *Tisdale et al.,* who assessed the effect of intravenous haloperidol on QT interval dispersion in critically ill patients who received intravenous haloperidol for delusional agitation. QTc intervals were measured, and QT interval dispersion was calculated.

Haloperidol prolonged QTc interval compared to pretreatment values in Torsades de Pointes patients by a greater magnitude than in patients who did not experience Torsades de Pointes. It was concluded that intravenous haloperidol prolongs QTc intervals in critically ill patients [19].

Also, there was a significant decrease in Hemoglobin levels and total leucocytic count after 48 h from haloperidol therapy. Possible reasons for that decrease of the total leucocytic count are that TLC was elevated on day 0 of drug initiation due to sepsis which decreased with starting broad-spectrum antibiotics & control of sepsis. Also, the possible reasons for decreased level of hemoglobin are dilutional effect of intravenous fluids, blood sampling for lab and bone marrow suppression from sepsis.

References

1. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med. 2009; 37(12):3031-9. https://doi.org/10.1097/CCM.0b013e3181b02eff PMid:19633543

2. Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs. 2012; 72(14):1881-916. https://doi.org/10.2165/11636220-000000000-00000 PMid:22950534

3. Weinert CR, Calvin AD. Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit. Crit Care Med. 2007; 35(2):393-401. https://doi.org/10.1097/01.CCM.0000254339.18639.1D PMid:17205015

4. Riker RR, Fraser GL. Adverse events associated with sedatives, analgesics, and other drugs that provide patient comfort in the intensive care unit. Pharmacotherapy. 2005; 25(5 Pt 2):8S-18S. https://doi.org/10.1592/phco.2005.25.5_Part_2.8S PMid:15899744

5. Gagnon DJ, Riker RR, Glisic EK, Kelner A, Perrey HM, Fraser GL. Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study. Pharmacotherapy. 2015; 35(3):251-9. https://doi.org/10.1002/phar.1559 PMid:25809176

6. Fraser GL, Riker RR. Phenobarbital provides effective sedation for a select cohort of adult ICU patients intolerant of standard treatment: a brief report. Hosp Pharm. 2006; 41:17-23. https://doi.org/10.1310/hpj4101-17

7. Seeman P. Atypical neuroleptics: role of multiple receptors, endogenous dopamine, and receptor linkage. Acta Psychiatr Scand Suppl. 1990; 358:14-20. https://doi.org/10.1111/j.1600-0447.1990.tb05280.x PMid:1978482

8. Fraser Gl et al. Haloperidol should be used sparingly. Crit Care Med. 2002; 30(11):2614. https://doi.org/10.1097/00003246-200211000-00052

9. Hassaballa HA, Balk RA. Torsade de pointes associated with the administration of intravenous haloperidol. Am J Ther. 2003; 10(1):58-60. https://doi.org/10.1097/00045391-200301000-00013

10. Perucca E. Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. CNS Drugs. 2002; 16(10):695-714. https://doi.org/10.2165/00023210-200216100-00004 PMid:12269862

11. Rosenberg G. The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? Cell Mol Life Sci. 2007; 64(16):2090-103. https://doi.org/10.1007/s00018-007-7079-x PMid:17514356

12. Bourgeois JA, Koike AK, Simmons JE, Telles S, Eggleston C. Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. J Neuropsychiatry Clin Neurosci. 2005; 17(2):232-8. https://doi.org/10.1176/jnp.17.2.232 PMid:15939979

13. Sher Y, Miller AC, Lolak S, Ament A, Maldonado JR. Adjunctive valproic acid in management-refractory hyperactive delirium: a case series and rationale. J Neuropsychiatry Clin Neurosci. 2015; 27(4):365-70. https://doi.org/10.1176/appi.neuropsych.14080190 PMid:25803136

14. Fitz K, Harding A. Safety and efficacy of valproic acid for treatment of delirium in critically ill patients [abstract]. Crit Care Med. 2011; 39(Suppl. 12):239.

15. Danan, et al. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. Journal of clinical epidemiology. 1993; 46(11):1323-1330. https://doi.org/10.1016/0895-4356(93)90101-6

16. Gagnon DJ, Fontaine GV, Smith KE, Riker RR, Miller III, Lerwick PA, et al. Valproate for agitation in critically ill patients: a retrospective study. Journal of critical care. 2017; 37:119-125. https://doi.org/10.1016/j.jcrc.2016.09.006 PMid:27693975

17. Riker RR, Richard R, GILLES L. Fraser, and Paul M. Cox. Continuous infusion of haloperidol controls agitation in critically ill patients. Critical care medicine. 1994; 22(3):433-440. https://doi.org/10.1097/00003246-199403000-00013 PMid:8124994

18. Sinha, Shobhit, and Dean K. Naritoku. Intravenous valproate is well tolerated in unstable patients with status epilepticus. Neurology. 2000; 55(5):722-724. https://doi.org/10.1212/WNL.55.5.722 PMid:10980746

19. Tisdale JE, Rasty S, Padhi ID, Sharma ND, Rosman H. The effect of intravenous haloperidol on QT interval dispersion in critically ill patients: comparison with QT interval prolongation for assessment of risk of torsades de pointes. The Journal of Clinical Pharmacology. 2005; 41(12):1310-1318. https://doi.org/10.1177/009127001220128896 PMid:11762558