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Effects of valproic acid and magnesium sulphate on rocuronium requirement in patients undergoing craniotomy for cerebrovascular surgery

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Editor's key points

- Anti-epileptic drugs are known to cause resistance to non-depolarizing neuromuscular blocking agents.
- The authors tested the hypothesis that valproic acid (VPA) increases resistance to rocuronium.
- The findings of this study suggest that VPA increased the resistance to rocuronium and magnesium reversed this effect.
- The findings are important to understand clinically important drug interactions between VPA, magnesium, and rocuronium.

Background. Many anti-epileptics cause resistance to non-depolarizing neuromuscular blocking agents, but this has not been reported for valproic acid (VPA). We hypothesized that VPA would increase the rocuronium requirement and that magnesium sulphate ($MgSO_4$) may reduce this increase.

Methods. Fifty-five patients undergoing cerebrovascular surgeries were studied. Subjects were allocated into three groups at a 1:1:1 ratio: Groups VM, VC, and C. Groups VM and VC were given VPA premedication; Group C was not. A rocuronium injection (0.6 mg kg^{-1} i.v.) was administered to Group VM, followed by $MgSO_4$ as a 50 mg kg^{-1} i.v. bolus and 15 mg kg^{-1} h^{-1} infusion. The same volume of 0.9% saline was administered to the other groups. Supplementary rocuronium (0.15 mg kg^{-1}) was given whenever the train-of-four count reached 2. Rocuronium requirements (primary outcome), mean arterial pressure (MAP), heart rate (HR), nausea, vomiting, shivering, and use of anti-emetics and nicardipine were compared.

Results. Group VC showed the highest rocuronium requirement [mg kg^{-1} h^{-1}: 0.47 (0.08) *vs* 0.33 (0.12) (Group C), 0.31 (0.07) (Group VM); $P<0.001$]. MAP, intraoperative HR, nausea, vomiting, shivering, and use of anti-emetics and nicardipine were not significantly different among the groups. Postoperative HR was lower in Group VM than in Group VC.

Conclusions. VPA increased the rocuronium requirement, and $MgSO_4$ infusion attenuated this increase.

Keywords: anti-convulsant, valproic acid; ions, magnesium; neuromuscular block, rocuronium

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Many antiepileptic drugs induce resistance to non-depolarizing muscle relaxants (NDMRs).[1] An accelerated reversal from NDMRs in patients undergoing surgery can be serious because of unintended patient movements that can interfere with surgical procedures and compromise patient safety.

Effects of valproic acid (VPA) on the duration of NDMRs have not been reported to date. VPA is a commonly used antiepileptic with extended indications in cancer, acquired immunodeficiency syndrome, Alzheimer's disease, migraine, and bipolar disorder.[2] Therefore, in this study, we measured the rocuronium requirement (primary outcome) in VPA-premedicated patients undergoing cerebrovascular surgeries, with the primary hypothesis that VPA decreases rocuronium duration, and thus increases its requirement.

Magnesium sulphate ($MgSO_4$) is known to potentiate the effects of NDMRs.[3] Thus, we hypothesized that the possible VPA-induced increase in rocuronium requirements is attenuated by $MgSO_4$.

Methods

This double-blind randomized controlled trial was approved by the Institutional Review Board and was registered at ClinicalTrials.gov (ID: NCT01460563). Written informed consent was obtained from all participants (age range, 18–65 yr; ASA I–II) undergoing elective craniotomy for aneurysm clipping or for superficial temporal artery–middle cerebral artery anastomosis (Fig. 1). Exclusion criteria were: BMI<18.5 or >24.9 kg m^{-2}; neuromuscular, renal, cardiovascular, or hepatic insufficiency; Glasgow coma scale (GCS) <15; allergy to the study drugs; medications influencing NDMRs, such as corticosteroids, aminoglycosides, furosemide, antiepileptics other than VPA; breastfeeding; pregnancy; and preoperative epilepsy (Table 1).

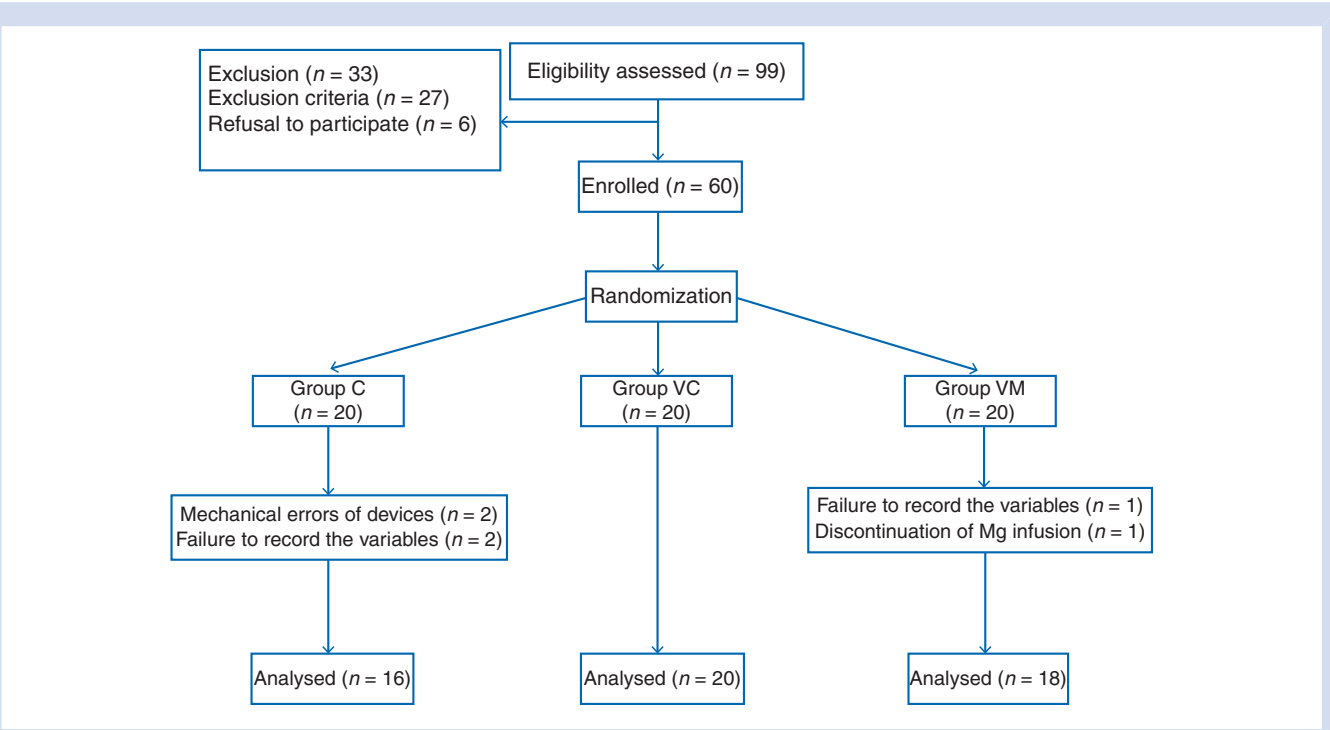

Fig 1 Flow diagram of the study participants. Group C, control group; Group VC, VPA-control group; Group VM, VPA-magnesium group.

Subjects were randomly allocated into three groups, using opaque sealed envelopes: VPA-$MgSO_4$ (Group VM: VPA premedication and $MgSO_4$ infusion), VPA control group (Group VC; VPA premedication and no $MgSO_4$ infusion), and control group (Group C; no VPA premedication and no $MgSO_4$ infusion). VPA users were administered sodium valproate 1200 and 600 mg i.v. 9 and 2 h before surgery, respectively. Group allocation was coded and concealed until the statistical analyses were complete. The study drugs were prepared and labelled (blue, $MgSO_4$; red, placebo saline) by a nurse who was unaware of the study design. Research personnel who recorded the study variables or who gave the drugs to the patients were blinded to group allocation, study design, and drugs.

The serum VPA concentration was measured immediately before anaesthetic induction in VPA users. Total i.v. anaesthesia was maintained with target-controlled infusion of propofol, titrated to maintain a bispectral index of 40–60. If mean arterial pressure (MAP) or heart rate (HR) changed to $<$80% or $>$120% of baseline values, remifentanil was titrated at first, and then propofol was titrated, if necessary.

Neuromuscular monitoring adhered to the clinical research consensus.[4] Two paediatric surface electrodes were placed 4 cm apart over the cleansed skin along the ulnar nerve on the side without either an intravascular line or an arterial pressure cuff. The four fingers and the forearm were immobilized, and the position of the acceleration transducer was secured by placing the thumb in a hand adapter (Organon Ltd, Dublin, Ireland). Using a train-of-four (TOF) Watch SX® (Organon Ltd), after a few 2 Hz TOF stimulations (stimulus duration of 200 μs, square wave) and 50 Hz tetanus for 5 s, calibration (implanted mode 2) and stable TOF responses ($<$5% deviation for 2 min) were ensured in sequence, followed by 2 Hz TOF every 15 s. A rectal temperature $>$35°C and skin temperature on the volar side of the thenar $>$32°C were maintained during the operation.

Subsequently, rocuronium (0.6 mg kg^{-1}, i.v.) was administered for tracheal intubation, and patients in Group VM received $MgSO_4$ 50 mg kg^{-1} as an i.v. bolus for 10 min, followed by continuous infusion at 15 mg kg^{-1} h^{-1}. In Groups C and VC, 0.9% saline was administered in the same manner as in Group VM. Intraoperative monitoring included ECG, arterial pressure (radial artery cannulation), central venous pressure, and urinary output.

Supplementary rocuronium (0.15 mg kg^{-1}) was administered whenever the TOF count reached 2 during the surgery. The intervals between rocuronium (0.15 mg kg^{-1}) injections were measured. Ionized Mg (Mg^{2+}) was measured at baseline, 3 h, and immediately after surgery. MAP and HR were recorded at baseline, at intubation, at 5 and 15 min, and every 30 min afterwards until the end of surgery, and then at 1, 3, 5, 8, 16, 24, 32, and 48 h after surgery. Ventilation was maintained with 50% oxygen in air and with an end-tidal CO_2 of 4.7–5.3 kPa.

After the operation, patients were given i.v. midazolam (3 mg) and rocuronium (20 mg) for subsequent postoperative radiologic brain imaging, and then transferred to the intensive care unit where they were extubated. The GCS was

Table 1 Patient and surgery characteristics. Data are numbers (%), means (SD), or medians (inter-quartile range). Group C, control group; Group VC, VPA-control group; Group VM, VPA-Mg group; VPA, valproic acid. *Superficial temporal artery–middle cerebral artery anastomosis. †Cerebral artery stenosis of non-Moyamoya origin. ‡J.B. and C.O. are the initial letters of the surgeons' names

Characteristic	Group C ($n=16$)	Group VC ($n=20$)	Group VM ($n=18$)
Age (yr)	53 (18-65)	52 (20-65)	53 (21-65)
Gender (M/F)	7 (44%)/9 (56%)	9 (45%)/11 (55%)	9 (50%)/9 (50%)
Body weight (kg)	38.2 (6.2)	60.5 (6.8)	59.6 (10.1)
Height (cm)	159.7 (6.7)	161.5 (6.9)	161.6 (10.1)
BMI (kg m^{-2})	22.9 (2.1)	23.2 (1.8)	22.7 (2.1)
ASA (I/II)	7 (44%)/9 (56%)	6 (30%)/14 (70%)	8 (44%)/10 (56%)
Operation			
Aneurysm clipping	11 (69%)	14 (70%)	14 (78%)
MCA–STA anastomosis*	5 (31%)	6 (30%)	4 (22%)
Diagnosis			
Aneurysm	11 (69%)	14 (70%)	14 (78%)
Moyamoya disease	2 (12%)	3 (15%)	2 (11%)
Artery stenosis†	3 (19%)	3 (15%)	2 (11%)
Surgeon (J.B./C.O.)‡	7 (44%)/9 (56%)	9 (45%)/11 (55%)	9 (50%)/9 (50%)
Anaesthesia time (min)	337 (102)	349 (119)	334 (115)
Operation time (min)	263 (102)	273 (106)	270 (112)
Blood loss (ml)	340 (178–575)	305 (270–400)	400 (288–563)
Serum VPA (μg ml^{-1})	Not applicable	76.35 (24.7)	83.53 (19.0)

evaluated at 6 h after operation. Patients received ramosetron (0.3 mg i.v.), followed by patient-controlled analgesia using fentanyl 2000 μg in 0.9% saline (total volume 100 ml) with a basal infusion of 1 ml h^{-1}, a bolus infusion of 1 ml, and a lock-out time of 10 min. Rescue anti-emetics (ramosetron 0.3 mg i.v.) were given, if necessary. Nicardipine i.v. were used to maintain 80–120% of baseline MAP during the postoperative 48 h. Adverse effects related to $MgSO_4$, including respiratory difficulty and arrhythmia, were observed throughout the study period. Drug preparation and collection/measurement/analysis of data were performed by doctors, nurses, and research assistants, who were all blinded to the study.

The sample size calculation was based on the unpublished VPA user pilot data, which required rocuronium 0.43 (0.12) mg kg^{-1} h^{-1}. Accepting a 30% reduction in rocuronium in the controls to be significant, 20 patients per group were required according to a two-sided test with $\alpha=0.05$ and $\beta=0.2$, allowing for 20% drop-outs. Data are expressed as numbers of patients (%), means (SD), or medians (inter-quartile range) (for skewed data). Analysis of variance (ANOVA) was performed for comparison of continuous variables such as doses of rocuronium and anaesthetics. As for measurements over time (temperature, MAP, HR, and Mg^{2+} concentration), if there were statistical differences by repeated-measures ANOVA, independent *t*-test or ANOVA was used for comparison at each time point. The Bonferroni test was used for *post hoc* analysis. Categorical data were analysed with the χ^2 test or Fisher's exact test, as indicated. The Mann–Whitney *U*-test or the Kruskal–Wallis test was substituted for the *t*-test or ANOVA, respectively, for skewed data. Statistical analyses were performed with PASW Statistics 17 release version 17.0.2 (SPSS, Inc., Chicago, IL, USA). Values of $P<0.05$ indicated significance.

Results

Group VC required a significantly higher total dose of rocuronium and showed a shorter interval between rocuronium (0.15 mg kg^{-1}) injections (Table 2). There were no significant differences in the rocuronium requirement and injections interval between Groups C and VM ($P>0.05$). Intraoperative rectal and skin temperatures, MAP, and HR were comparable among the groups (Figs 2–4).

MAP was also comparable after operation, but HR was significantly lower in Group VM than that in Group VC ($P=0.02$) (Figs 3 and 4). No statistical difference was found in HR between Groups VM and C or between Groups VC and C ($P>0.05$). The postoperative incidence of and dose of nicardipine use were, respectively, 10 (63%) and 0.8 (0–6.4) in Group C, and 13 (65%) and 1 (0–9.4) mg in Group VC, and 6 (33%) and 0 (0–1.4) mg in Group VM ($P>0.05$ for incidence and dose, respectively). Magnesium-related side-effects were not seen in any participant.

Discussion

VPA pre-treatment increased the rocuronium requirement compared with that in the controls. VPA induces the expression of MDR1, a gene encoding a P-glycoprotein (Pgp).[5] Pgp mediates biliary excretion of rocuronium in a rat model.[6] Biliary excretion is a major route of rocuronium elimination.[7] Therefore, it is conceivable that VPA increases Pgp activity,

Table 2 Dose of rocuronium and anaesthetics, serum magnesium concentration, and postoperative data. Data are means (SD) or numbers (%). *$P<0.001$, †$P<0.01$ *vs* all other groups. ‡Time from the end of the surgery to tracheal extubation. Mg^{2+} is expressed in mmol litre^{-1}. Group C, control group; Group VC, VPA-control group; Group VM; VPA-Mg group; Roc, rocuronium; GCS, Glasgow coma scale

Parameter	Group C ($n=16$)	Group VC ($n=20$)	Group VM ($n=18$)	*P*-value
Total Roc dose (mg kg^{-1} h^{-1})	0.33 (0.12)	0.47 (0.08)*	0.31 (0.07)	<0.001
Roc injections interval (min)	39 (13)	24 (4)†	36 (13)	<0.001
Propofol (mg kg^{-1} h^{-1})	8.9 (1.8)	8.9 (2.7)	7.7 (3.0)	0.276
Remifentanil (μg kg^{-1} min^{-1})	0.073 (0.037)	0.087 (0.051)	0.078 (0.029)	0.563
Serum Mg^{2+} concentration				
Baseline	052 (0.04)	0.50 (0.03)	0.51 (0.03)	0.147
After 3 h	0.51 (0.04)	0.48 (0.03)	0.73 (0.1)*	<0.001
Immediate postoperative	0.51 (0.06)	0.5 (0.05)	0.78 (0.1)*	<0.001
Extubation time (min)‡	226 (188)	241 (155)	186 (205)	0.44
GCS at postoperative 6 h	10.9 (4.5)	10.8 (4.4)	11.0 (4.5)	0.55
Nausea (*n*)	6 (38%)	11 (55%)	7 (39%)	0.49
Vomiting (*n*)	3 (19%)	6 (30%)	1 (6%)	0.15
Shivering (*n*)	3 (19%)	5 (25%)	0	0.08
Use of anti-emetics (*n*)	5 (31%)	9 (45%)	6 (33%)	0.64

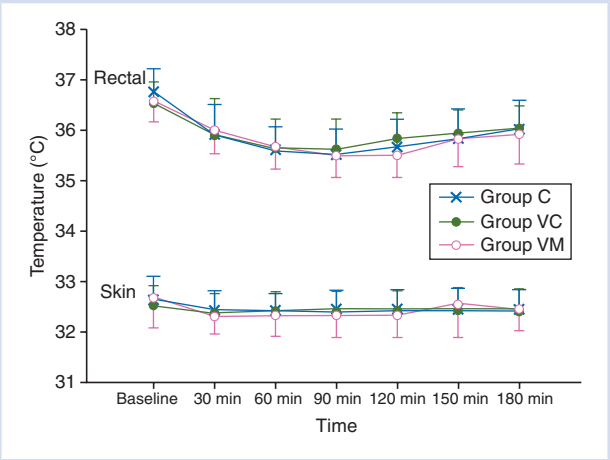

Fig 2 Changes in intraoperative rectal (upper) and skin (lower) temperature. Data are means (SD). Group C, control group; Group VC, VPA-control group; Group VM, VPA-magnesium group.

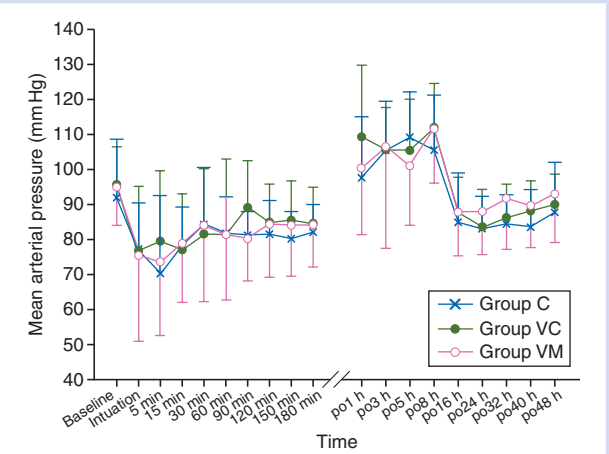

Fig 3 Changes in MAP. Data are means (SD). Group C, control group; Group VC, VPA-control group; Group VM, VPA-magnesium group.

leading to facilitated biliary excretion of rocuronium. Accelerated recovery from rocuronium should be noted in anaesthetic management, particularly for patients undergoing a craniotomy whose head is fixed with pinning devices, because inadvertent movements may result in brain tissue injury or intracranial haemorrhage.

This is the first study that has investigated VPA-induced decrease in the duration of NDMRs. A case report described accelerated rocuronium reversal in one patient receiving both VPA and primidone, but the causative agents were unclear.[8] The suggested mechanisms of anticonvulsant-induced resistance to NDMRs include increases in cytochrome P-450 isoenzymes[9 10] and in α1-acid glycoprotein.[1 9 10] However, some studies reported that VPA inhibits[11] or does not increase[12] the isoenzymes. No evidence of increased α1-acid glycoprotein levels with VPA treatment has been observed.

In contrast, acute exposure to VPA induces partial neuromuscular block *in vitro*.[13] This could also account for rocuronium resistance, because such antagonism may cause up-regulation of acetylcholine (Ach) receptors.[1 8 10] If VPA induced neuromuscular block in our study, it might have reduced the magnitude of the TOF twitch response. However, VPA-induced neuromuscular block is subclinical and does not potentiate the effects of NDMRs.[13]

Acute administration of anti-epileptics causes neuromuscular block,[10] whereas chronic treatment induces resistance to NDMRs.[1] However, in our study, the first exposure to VPA

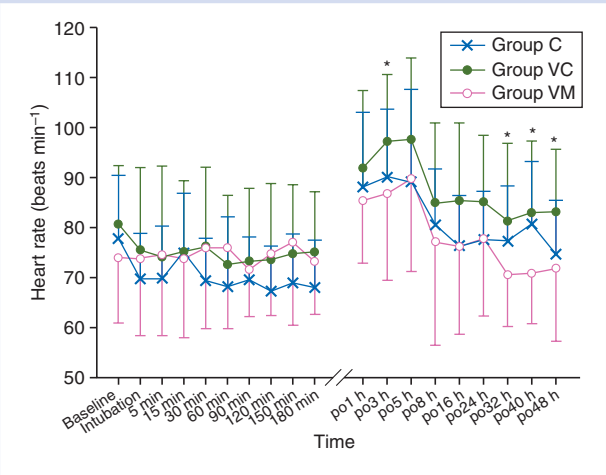

Fig 4 Changes in HR. Data are means (SD). Group C, control group; Group VC, VPA-control group; Group VM, VPA-magnesium group. *$P<0.05$ Groups VC *vs* VM.

was 9 h before the operation. Additionally, VPA treatment for 2–7 days resulted in increased MDR1 expression in rat liver cells.[12] Hence, anaesthetists' consideration for increased rocuronium requirement should not be limited to prolonged administration of VPA.

Patients with epilepsy were excluded from our study because they were likely to have an elevated initial level of Pgp.[14] VPA use in these patients could further increase Pgp and consequently potentiate the acceleration of rocuronium reversal. This should be noted during anaesthetic management of patients with epilepsy, as VPA is a frequently used anticonvulsant.[2]

In the present study, the VPA-induced increase in the rocuronium requirement was reduced to control levels by $MgSO_4$. Magnesium potentiates NDMRs mainly by decreasing prejunctional Ach release.[15] As rocuronium is a competitive antagonist of Ach, the Mg-induced Ach reduction may offset the rocuronium elimination facilitated by VPA. Thus, $MgSO_4$ administration may reduce the risk for unexpected movements caused by accelerated rocuronium reversal. Additionally, $MgSO_4$ decreased the frequency of rocuronium injections in VPA users in this study, which may improve anaesthetists' convenience.

The use of $MgSO_4$ may have another advantage in terms of postoperative analgesia by antagonizing the NMDA receptor, preventing enhanced NMDA signalling, and inhibiting calcium conductance.[15] In previous studies,[3 16] intraoperative $MgSO_4$ infusion provided pain relief during the immediate postoperative 48 h. The analgesic effects might have led to significantly lower HR in Group VM compared with Group VC in the present study. However, postoperative MAP was comparable between the groups. One possible explanation is that nicardipine controls hypertension, but cannot stabilize HR.[17]

The administration of $MgSO_4$ did not cause symptoms of hypermagnesemia in the present study, consistent with our previous reports.[3 16 18] In the previous reports, the same dose of $MgSO_4$ was used, and the immediate postoperative Mg concentration was 1.3–1.5, which decreased to 1.06 at 6 h after operation. The reference range of Mg (mmol litre^{-1}) is 0.7–1.3, and the therapeutic ranges are 1.1–1.5 for preeclampsia[19] and 2–2.5 for subarachnoid haemorrhage.[20] Thus, Mg^{2+} concentrations (mean, 0.78; maximum, 0.93) in our patients are considered below toxic level. Moreover, patients undergoing cerebrovascular surgery can be at risk for hypomagnesemia owing to the use of diuretics[21] and polyuria.[15 22] However, Mg-related possible complications should be considered, particularly in renal insufficiency.[15]

Comparable extubation times and postoperative GCSs among the groups in this study (Table 2) suggest that $MgSO_4$ may not necessarily affect postoperative recovery. In our previous study, time from skin closure to tracheal extubation was not prolonged when $MgSO_4$ was used intraoperatively in the same dose and regimen with that of the present study.[16] In addition, $MgSO_4$ 60 mg kg^{-1} delayed reversal of rocuronium-induced neuromuscular block from 24.7 (control) to 28.5 min.[23] Such delay may not have a significant clinical impact on surgeries of long duration, including cerebrovascular surgeries. However, $MgSO_4$ can possibly delay postoperative recovery,[24] and therefore patients receiving $MgSO_4$ during the surgery may require close observation during the recovery period.

One limitation of this study is that the effect of VPA on rocuronium onset was not measured, which might have further elucidated VPA effects on rocuronium resistance, had it been measured. As for the effect of magnesium, it was recently reported that rocuronium onset was accelerated by $MgSO_4$.[23]

In conclusion, VPA increased the rocuronium requirement, and intraoperative $MgSO_4$ infusion attenuated this increase.

Declaration of interest

None declared.

References

1 Naguib M, Lien C. Pharmacology of muscle relaxants and their antagonists. In: Miller RD, ed. *Miller's Anesthesia*. Philadelphia: Churchill Livingstone Elsevier, 2009; 859–911

2 Terbach N, Shah R, Kelemen R, *et al.* Identifying an uptake mechanism for the antiepileptic and bipolar disorder treatment valproic acid using the simple biomedical model dictyostelium. *J Cell Sci* 2011; **124**: 2267–76

3 Na HS, Lee JH, Hwang JY, *et al.* Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy. *Br J Anaesth* 2010; **104**: 344–50

4 Fuchs Buder T, Claudius C, Skovgaard L, Eriksson L, Mirakhur R, Viby Mogensen J. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. *Acta Anaesthesiol Scand* 2007; **51**: 789–808

5 Cerveny L, Svecova L, Anzenbacherova E, *et al.* Valproic acid induces CYP3A4 and MDR1 gene expression by activation of constitutive androstane receptor and pregnane X receptor pathways. *Drug Metab Dispos* 2007; **35**: 1032–41

6 Smit JW, Duin E, Steen H, Oosting R, Roggeveld J, Meijer DK. Interactions between P-glycoprotein substrates and other cationic drugs at the hepatic excretory level. *Br J Pharmacol* 1998; **123**: 361–70

7 Proost JH, Eriksson LI, Mirakhur RK, Roest G, Wierda JM. Urinary, biliary and faecal excretion of rocuronium in humans. *Br J Anaesth* 2000; **85**: 717–23

8 Driessen JJ, Robertson EN, Booij LH, Vree TB. Accelerated recovery and disposition from rocuronium in an end-stage renal failure patient on chronic anticonvulsant therapy with sodium valproate and primidone. *Br J Anaesth* 1998; **80**: 386–8

9 Soriano SG, Sullivan LJ, Venkatakrishnan K, Greenblatt DJ, Martyn JA. Pharmacokinetics and pharmacodynamics of vecuronium in children receiving phenytoin or carbamazepine for chronic anticonvulsant therapy. *Br J Anaesth* 2001; **86**: 223–9

10 Soriano SG, Martyn JA. Antiepileptic-induced resistance to neuromuscular blockers: mechanisms and clinical significance. *Clin Pharmacokinet* 2004; **43**: 71–81

11 Wen X, Wang JS, Kivisto KT, Neuvonen PJ, Backman JT. In vitro evaluation of valproic acid as an inhibitor of human cytochrome P450 isoforms: preferential inhibition of cytochrome P450 2C9 (CYP2C9). *Br J Clin Pharmacol* 2001; **52**: 547–53

12 Eyal S, Lamb JG, Smith-Yockman M, *et al.* The antiepileptic and anticancer agent, valproic acid, induces P-glycoprotein in human tumour cell lines and in rat liver. *Br J Pharmacol* 2006; **149**: 250–60

13 Nguyen A, Ramzan I. In vitro neuromuscular effects of valproic acid. *Br J Anaesth* 1997; **78**: 197–200

14 Lazarowski A, Czornyj L, Lubienieki F, Girardi E, Vazquez S, D'Giano C. ABC transporters during epilepsy and mechanisms underlying multidrug resistance in refractory epilepsy. *Epilepsia* 2007; **48** (Suppl. 5): 140–9

15 Herroeder S, Schonherr ME, De Hert SG, Hollmann MW. Magnesium—essentials for anesthesiologists. *Anesthesiology* 2011; **114**: 971–93

16 Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. *Br J Anaesth* 2008; **100**: 397–403

17 Lambert CR, Hill JA, Nichols WW, Feldman RL, Pepine CJ. Coronary and systemic hemodynamic effects of nicardipine. *Am J Cardiol* 1985; **55**: 652–6

18 Ryu JH, Sohn IS, Do SH. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. *Br J Anaesth* 2009; **103**: 490–5

19 Dasgupta A, McLemore JL. Elevated free phenytoin and free valproic acid concentrations in sera of patients infected with human immunodeficiency virus. *Ther Drug Monit* 1998; **20**: 63–7

20 Westermaier T, Stetter C, Vince GH, *et al.* Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: a randomized, placebo-controlled, clinical study. *Crit Care Med* 2010; **38**: 1284–90

21 Korenkov AI, Pahnke J, Frei K, *et al.* Treatment with nimodipine or mannitol reduces programmed cell death and infarct size following focal cerebral ischemia. *Neurosurg Rev* 2000; **23**: 145–50

22 Takaku A, Shindo K, Tanaka S, Mori T, Suzuki J. Fluid and electrolyte disturbances in patients with intracranial aneurysms. *Surg Neurol* 1979; **11**: 349–56

23 Czarnetzki C, Lysakowski C, Elia N, Tramer M. Time course of rocuronium induced neuromuscular block after pre treatment with magnesium sulphate: a randomised study. *Acta Anaesthesiol Scand* 2010; **54**: 299–306

24 Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. *Anaesthesia* 2006; **61**: 1058–63