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

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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 rocuroonium requirement and that magnesium sulphate (MgSO4) 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 rocuroonium injection (0.6 mg kg$^{-1}$ i.v.) was administered to Group VM, followed by MgSO4 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 rocuroonium (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 rocuroonium 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 rocuroonium requirement, and MgSO4 infusion attenuated this increase.

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

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Many anti-epileptic drugs induce resistance to non-depolarizing muscle relaxants (NDMRs). 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. Therefore, in this study, we measured the rocuroonium requirement (primary outcome) in VPA-premedicated patients undergoing cerebrovascular surgeries, with the primary hypothesis that VPA decreases rocuroonium duration, and thus increases its requirement.

MgSO4 is known to potentiate the effects of NDMRs. Thus, we hypothesized that the possible VPA-induced increase in rocuroonium requirements is attenuated by MgSO4.

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).
Subjects were randomly allocated into three groups, using opaque sealed envelopes: VPA-MgSO₄ (Group VM: VPA premedication and MgSO₄ infusion), VPA control group (Group VC; VPA premedication and no MgSO₄ infusion), and control group (Group C; no VPA premedication and no MgSO₄ 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, MgSO₄; 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. 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 MgSO₄ 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 (Mg²⁺) 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 CO₂ 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

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**Fig 1** Flow diagram of the study participants. Group C, control group; Group VC, VPA-control group; Group VM, VPA-magnesium group.
evaluated at 6 h after operation. Patients received ramose-tron (0.3 mg i.v.), followed by patient-controlled analgesia using fentanyl 2000
mg in 0.9% saline (total volume 100
ml) with a basal infusion of 1 ml h
superscript 2
, 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 MgSO4, 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
superscript 2
 h
superscript -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 (so), 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
superscript 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 \( \chi^2 \) 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 (0.15 mg kg
superscript -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 1** Patient and surgery characteristics. Data are numbers (%), means (so), 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group C (n = 16)</th>
<th>Group VC (n = 20)</th>
<th>Group VM (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53 (18-65)</td>
<td>52 (20-65)</td>
<td>53 (21-65)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>7 (44%)/9 (56%)</td>
<td>9 (45%)/11 (55%)</td>
<td>9 (50%)/9 (50%)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>38.2 (6.2)</td>
<td>60.5 (6.8)</td>
<td>59.6 (10.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.7 (6.7)</td>
<td>161.5 (6.9)</td>
<td>161.6 (10.1)</td>
</tr>
</tbody>
</table>
| BMI (kg m
superscript -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 (\( \mu g \) ml
superscript -1
) | Not applicable  | 76.35 (24.7)     | 83.53 (19.0)      |
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 isoenzymes9,10 and in α1-acid glycoprotein.19 However, some studies reported that VPA inhibits11 or does not increase12 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

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. Mg2+ 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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group C (n = 16)</th>
<th>Group VC (n = 20)</th>
<th>Group VM (n = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Roc dose (mg kg−1 h−1)</td>
<td>0.33 (0.12)</td>
<td>0.47 (0.08)*</td>
<td>0.31 (0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Roc injections interval (min)</td>
<td>39 (13)</td>
<td>24 (4)†</td>
<td>36 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Propofol (mg kg−1 h−1)</td>
<td>8.9 (1.8)</td>
<td>8.9 (2.7)</td>
<td>7.7 (3.0)</td>
<td>0.276</td>
</tr>
<tr>
<td>Remifentanil (μg kg−1 min−1)</td>
<td>0.073 (0.037)</td>
<td>0.087 (0.051)</td>
<td>0.078 (0.029)</td>
<td>0.563</td>
</tr>
</tbody>
</table>

Measurement of Mg2+ concentration

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group VC</th>
<th>Group VM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.52 (0.04)</td>
<td>0.50 (0.03)</td>
<td>0.51 (0.03)</td>
<td>0.147</td>
</tr>
<tr>
<td>After 3 h</td>
<td>0.51 (0.04)</td>
<td>0.48 (0.03)</td>
<td>0.73 (0.1)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Immediate postoperative</td>
<td>0.51 (0.06)</td>
<td>0.5 (0.05)</td>
<td>0.78 (0.1)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Exsanguine time (min)†</td>
<td>226 (188)</td>
<td>241 (155)</td>
<td>186 (205)</td>
<td>0.44</td>
</tr>
<tr>
<td>GCS at postoperative 6 h</td>
<td>10.9 (4.5)</td>
<td>10.8 (4.4)</td>
<td>11.0 (4.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Nausea (n)</td>
<td>6 (38%)</td>
<td>11 (55%)</td>
<td>7 (39%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vomiting (n)</td>
<td>3 (19%)</td>
<td>6 (30%)</td>
<td>1 (6%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Shivering (n)</td>
<td>3 (19%)</td>
<td>5 (25%)</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>Use of anti-emetics (n)</td>
<td>5 (31%)</td>
<td>9 (45%)</td>
<td>6 (33%)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

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.
Valproic acid, magnesium, and rocuronium

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.16 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 MgSO4. 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, MgSO4 administration may reduce the risk for unexpected movements caused by accelerated rocuronium reversal. Additionally, MgSO4 decreased the frequency of rocuronium injections in VPA users in this study, which may improve anaesthetists’ convenience.

The use of MgSO4 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,16 intraoperative MgSO4 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 nicardpine controls hypertension, but cannot stabilize HR.17

The administration of MgSO4 did not cause symptoms of hypomagnesemia in the present study, consistent with our previous reports.3 16 18 In the previous reports, the same dose of MgSO4 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 preeclampsia19 and 2–2.5 for subarachnoid haemorrhage.20 Thus, Mg2+ 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 diuretics21 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 MgSO4 may not necessarily affect postoperative recovery. In our previous study, time from skin closure to tracheal extubation was not prolonged when MgSO4 was used intraoperatively in the same dose and regimen with that of the present study.16 In addition, MgSO4 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, MgSO4 can possibly delay postoperative recovery,24 and therefore patients receiving MgSO4 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 MgSO4.23

In conclusion, VPA increased the rocuronium requirement, and intraoperative MgSO4 infusion attenuated this increase.

Declaration of interest

None declared.

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