Effects of Flunarizine on Neurological Recovery and Spinal Cord Blood Flow in Experimental Spinal Cord Ischemia in Rabbits

Stephen H. Johnson, MD; Joyce M. Kraison, BS; Geoffrey M. Graeber, MD

Background and Purpose: The lipophilic calcium channel antagonist flunarizine has been demonstrated to be neuroprotective in several models of cerebral ischemia. Ischemic spinal cord injury may have a similar pathophysiology and hence may respond in a similar fashion. This study was designed to investigate the effects of pretreatment with flunarizine on systemic hemodynamics, spinal cord blood flow, and neurological recovery in a rabbit model of ischemic spinal cord injury.

Methods: New Zealand White rabbits were anesthetized with ketamine and xylazine and instrumented for systemic blood pressure monitoring and spinal cord blood flow measurements using the microsphere method. After pretreatment with flunarizine or vehicle, ischemic spinal cord injury was created selectively in the caudal regions of the spinal cord by cross-clamping the abdominal aorta for a period of 25 minutes. Spinal cord blood flow was measured before, during, and 15 minutes after cross-clamp removal. Animals were allowed to recover and were graded neurologically at 18 and 24 hours after ischemia.

Results: Flunarizine injection was associated with hypotension that was both transient and dose related. Animals pretreated with flunarizine 0.4 mg/kg had significantly improved neurological recovery scores at 18 hours after ischemia (P=.017) compared with vehicle controls. At 24 hours this effect was lessened (P=.095); however, 60% of flunarizine-treated animals retained their ability to hop, whereas all of the vehicle-treated animals were nonambulatory.

Conclusions: Flunarizine has a protective effect on neurological recovery after experimental ischemic spinal cord injury. The therapeutic window is narrow, and dosing is limited by untoward hypotension. The mechanism of protection likely involves inhibition of pathological cytotoxic calcium accumulation rather than a direct effect on vascular smooth muscle. (Stroke. 1993;24:1547-1553.)

Key WORDs • calcium channel blockers • neuroprotection • spinal cord • rabbits

Spinal cord ischemia may complicate aortic reconstructive procedures or direct spinal cord surgery for tumor or vascular malformation. Neuronal cell death after ischemia is dependent on the selective vulnerability of a given population of neurons and the intrinsic blood supply to those cells. Delayed cell death of neurons not immediately injured by the ischemic event is the result of a cascade of events mediated by the deleterious effects of free radical generation, lipid peroxidation, and the accumulation of intracellular calcium.1 Increases in cytosolic calcium have been shown to activate calcium-dependent degradative enzymes and, in specific nerve terminals, may stimulate the release of excitotoxic neurotransmitters.2 Both of these mechanisms could contribute to ongoing neuronal damage.3 There is a significant accumulation of data concerning the effects of calcium antagonists in cerebral ischemia.3-9 Few studies have examined their use in spinal cord ischemia models.10,11 Most investigations have been aimed at examining the effect of calcium antagonists in spinal cord injury models with secondary ischemia.12,15

A chemically distinct subgroup of calcium antagonist, the diphenylalkylamines, has been identified that is highly lipophilic and readily crosses the blood-brain barrier. Flunarizine (1-cinnamyl-4[(p-fluorophenyl)methyl] piperazine hydrochloride) is representative of this subgroup and has a receptor-mediated effect on vascular smooth muscle as well as a direct effect on contractile proteins in smooth muscle tissue.16 Flunarizine exhibits antivasospastic activity both in vitro and in vivo9,17,18 and is a potent vasodilator with a predilection for cerebral vessels.19 In a preliminary report flunarizine pretreatment improved neurological recovery after spinal cord ischemia in a rat model.10

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The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense (para 4-3, AR 360-5).

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The present study was undertaken to determine the effects of flunarizine on spinal cord blood flow (SCBF) and neurological recovery in a well-established model of spinal cord ischemia.

Materials and Methods

Animal Preparation

Research was conducted in accordance with the Animal Welfare Act and the federal statutes and regulations relating to animals and experiments involving animals and adheres to the principles set forth in the Guide for the Care and Use of Laboratory Animals, National Institutes of Health Publication 85-23, 1985. Forty-two male New Zealand White rabbits (body weight, 2.5 to 3.5 kg) were anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (8 mg/kg). The left ventricle was cannulated via the carotid artery with a 15-cm length of PE-60 tubing for the injection of microspheres. Presence of the injection catheter in the left ventricle of heart was confirmed and monitored by the presence of a characteristic left ventricular pressure tracing. The internal jugular vein was cannulated with an 8.5-cm length of PE-60 tubing for the administration of maintenance fluids, bicarbonate, and flunarizine. The distal aorta was cannulated via the femoral artery at the groin with a 20-cm segment of PE-60 tubing introduced 2 to 3 cm into the distal abdominal aorta for the measurement of distal systemic arterial blood pressure (DAP) and for reference blood withdrawal during microsphere studies. Proximal aortic blood pressure (PAP) was measured via PE-60 tubing introduced through the renal artery and 2 to 3 cm into the abdominal aorta. Renal artery cannulation sites were randomly altered from left to right to eliminate bias. PAP and DAP were measured by pressure transducer (Tektronix, Beaverton, Ore) and displayed online throughout the experiment. Arterial blood gases were obtained at 15-minute intervals throughout the experiment in most animals. Acidosis identified as pH less than 7.30 was corrected with intravenous sodium bicarbonate. Body temperature was maintained at 37° to 39°C using heating pads assisted by esophageal temperature monitoring. Spinal cord ischemia was produced by occluding the infrarenal abdominal aorta with a nontraumatic vascular clip for a period of 25 minutes (Fig 1). This method requires a midline, vertical abdominal laparotomy under clean operative technique. Clip placement was verified by noting a profound decrement in the DAP to a mean of 5 to 10 mm Hg.

Microsphere Technique

The reference microsphere technique was used for the measurement of both segmental SCBF (cervical, thoracic, and lumbar) and cardiac output (CO) and is described in detail elsewhere. Briefly, approximately 30 minutes after arterial catheterizations, a 0.5-mL microsphere suspension containing 800,000 to 1 million microspheres (3M Corp, St Paul, Minn) (15±2 μm in diameter) labeled with either 111In, 85Sr, 51Cr, or 95Nb was injected over 20 seconds via the left ventricular catheter, followed immediately by a 0.5-mL flush with heparinized saline. Reference blood withdrawal was begun 10 seconds before microsphere injection and was continued for a period of 75 seconds at a speed of 1 mL/min via the distal aortic cannula using rate-controlled constant withdrawal (Harvard Apparatus Co, Inc, South Natick, Mass). Three microsphere injections (10 minutes before ischemia, during ischemia at 20 minutes, and 15 minutes after ischemia) provided pres ischemic, ischemic, and posts ischemic SCBF and CO measurements, respectively. Injections of these numbers of microspheres were determined in pilot studies to yield at least 400 microspheres per sample. At the completion of the experiment tissue specimens were harvested and weighed. Radioactivity in the specimens was determined using a five-channel, universal gamma counter (Pharmacia/LKB Instruments, Piscataway, NJ). SCBF and CO were determined as relative to the activity of a reference (Ref) sample (R) where:

\[ R = \frac{cpm (Ref)}{Wt (Ref)} \]

Cardiac output was then determined as:

\[ CO = \frac{cpm (S)}{cpm (Syr)/R} \]

where S is standard, cpm is counts per minute, and Syr is syringe after injection. CO is expressed as milliliters per minute. Organ blood flow (BF) was then expressed in milliliters per minute per 100 g and determined as follows:

\[ BF = \frac{Sample cpm}{Sample Wt \times 100/R} \]

Spillover among isotope detection windows was determined using microsphere isotope standards, and appropriate corrections were made in all tissue samples. When estimates of blood flow between paired organs differed by more than 20%, inadequate ventricular mixing was assumed and the animal was removed from the study.

Experimental Design

Four treatment groups and one control group provided the data for this study. Flunarizine was administered by intravenous slow bolus injection at 0.1, 0.3, 0.4, or 1.0 mg/kg. Aqueous vehicle was administered in a similar fashion. Flunarizine was provided as a gift from A. Wauquier (Janssen Pharmaceutica, Beerse, Belgium). After baseline microsphere injection for blood flow determination, an intravenous bolus of flunarizine or vehicle was
injected over 5 to 10 minutes. The aorta was then occluded and the abdomen closed temporarily with towel clips. A second blood flow determination was made 5 minutes before clip removal. After clip removal the abdomen was sutured with 2-0 silk, and no further anesthetic was administered. Reperfusion blood flow was measured 15 minutes after clip removal. Blood pressure, heart rate, and CO measurements were obtained with every blood flow. After the final microsphere injection all cannulas were removed. Animals were caged and allowed to recover, during which time they were attended to and fed by technicians. Forced liquid bottle feeding was necessary in a few animals during the initial anesthesia recovery period. Once the anesthetic had worn off all animals ate and drank adequately.

**Neurological Assessment**

Neurological function was graded on a five-point ordinal scale (Table 1) at 18 and 24 hours after ischemia. An uninvolved technician and one of the principal investigators, both of whom were blinded as to treatment, graded functional recovery independently. Animals that appeared to be in severe distress at any time during the postischemic observation period (n=2) were euthanatized but included in the blood flow data. All paralyzed animals had to have their bladders emptied by manual decompression (Crède maneuver). Animals generally tolerated the experiment well, and mortality was low.

**Postmortem Studies**

Animals were euthanatized with T-61 solution 10 mg/kg IV (Taylor Pharmaceutical Co, Decatur, Ill). The spinal cord was harvested and divided into cervical, thoracic, and lumbar sacral segments for subsequent quantitative microsphere determinations. Both kidneys, both gonads, and brain halves were harvested, and blood flow data were used to assess equal streaming of microspheres by comparing relative blood flow to these paired organs.

**Data Analysis**

Differences between preischemic, ischemic, and postischemic segmental SCBF, CO, PAP, and DAP measurements were calculated for each rabbit. These data were then evaluated by analysis of variance, and significant differences among treatment group means were identified by the Newman-Keuls test. Neurological recovery scores for each treatment group were compared with vehicle controls using the Mann-Whitney test for unpaired nonparametric data. Significance was indicated at the level of *P*<.05 for all statistical analyses.

### TABLE 1. Neurological Recovery Grading Scale

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Hind-limb paralysis</td>
<td>0</td>
</tr>
<tr>
<td>Severe paraparesis</td>
<td>1</td>
</tr>
<tr>
<td>Functional movement, no hop</td>
<td>2</td>
</tr>
<tr>
<td>Ataxia, disconjugate hop</td>
<td>3</td>
</tr>
<tr>
<td>Minimal ataxia</td>
<td>4</td>
</tr>
<tr>
<td>Normal function</td>
<td>5</td>
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</table>

**Results**

Flunarizine had marked effects on systemic arterial blood pressure (SABP) immediately after infusion. Results are depicted in Fig 2. The most profound and potentially clinically relevant levels of hypotension were associated with the 0.4- and 1.0-mg/kg doses. There was an associated reflex tachycardia, but no ectopy or arrhythmias were noted. The mean duration of the hypotensive event was 5 to 7 minutes after completion of the infusion, with a mean decline in SABP of 20 mm Hg. Spinal cord ischemia was not created until animals returned to baseline SABP. The possibility that a microsphere injection might exacerbate the hypotension precluded the measurement of SCBF and CO during the episode. Neither flunarizine infusion nor hypotension appeared to lower body temperature, which was a time-dependent, ambient temperature–dependent phenomenon. There was no association between transient hypotension and mortality.

Pretreatment CO was similar in all groups, with a mean of 540 mL·min⁻¹·100 g⁻¹, although there was great individual variation and a large SD of the mean. Mean CO declined to 408 mL·min⁻¹·100 g⁻¹ during the ischemic period but returned to at or near baseline by 15 minutes of reperfusion.

Baseline SCBF to the cervical, thoracic, and lumbar sacral segments, reported as mean±SD, were 63±13.6, 42.5±13.8, and 53.3±10.6 mL·min⁻¹·100 g⁻¹, respectively. Mean cerebral blood flow was 100±27 mL·min⁻¹·100 g⁻¹ and was not significantly influenced by flunarizine at any dose. The ischemic insult resulted in a significant drop in SCBF at all levels of the spinal cord, but most severe in the lumbar sacral region. Cervical SCBF never declined below 25 mL·min⁻¹·100 g⁻¹, and flunarizine had no clear effect on ischemic or reperfusion blood flow. In the thoracic spinal cord, SCBF had a profile similar to that of lumbar sacral flows with mean ischemic SCBF near 20 mL·min⁻¹·100 g⁻¹ in all but the 0.3- and 0.4-mg/kg treatment groups, in which mean SCBF was maintained above 25 mL·min⁻¹·100 g⁻¹ (Fig 3). Reperfusion SCBF remained statistically quite lower than baseline in all comparison
groups. Lumbosacral SCBF demonstrated the most profound decrements in ischemic flow, measuring 10, 13.5, 18, and 24 mL·min⁻¹·100 g⁻¹ in the 0.1-mg/kg, 1.0-mg/kg, vehicle, and 0.3-mg/kg treatment groups, respectively. The 0.4-mg/kg treatment group had a higher mean SCBF, but a large SEM precluded statistical significance. Reperfusion SCBF to the caudal regions of the spinal cord, unlike the thoracic regions, returned to baseline with only the 1.0-mg/kg treatment group demonstrating reperfusion hyperemia measuring 150% of baseline blood flow. When compared with vehicle, flunarizine failed to significantly alter or preserve ischemic or reperfusion SCBF at any of the doses used, despite a trend toward improvement in the 0.4-mg/kg treatment group (Fig 4).

In our preliminary studies 88% of rabbits subjected to 25 minutes of ischemia were paraplegic at 24 hours. Twelve percent were grade 1 or 2. No animals were able to hop. There was no significant change in grade beyond 24 hours. In this hind-limb scores were evaluated at 18 and 24 hours. When comparing treatment groups with the vehicle-treated group at 18 hours, only the 0.4-mg/kg group had significantly better neurological scores (Mann-Whitney, two-tailed P = .017). When comparing treatment groups with vehicle at 24 hours this difference became less significant, with P = .095 (Table 2). However, when compared with vehicle controls at 24 hours, 60% of the 0.4-mg/kg treatment group animals were able to hop, although ataxic or dysconjugate, whereas no animals in the vehicle group could hop and most were completely paralyzed. Similarly, only one animal in each of the three remaining treatment groups retained the ability to hop 24 hours after ischemia. We did not attempt to correlate improved recovery with the level of ischemic SCBF or with the presence or absence of flunarizine-induced hypotension.

**Discussion**

Flunarizine is a highly lipophilic Ca²⁺ channel antagonist with selective action in arteries. Neuronal protection with this compound has been demonstrated in several cerebral ischemic and hypoxic models, but limited data exist regarding the use of flunarizine in spinal cord injury. Svennson et al reported an increase in postischemic SCBF but no improvement in functional recovery in flunarizine-treated baboons using an ischemic spinal cord injury model. A single pretreatment dose of 0.2 mg/kg was used in this study. Although we did not use this specific dose in our study, we were unable to see effects at similar low doses of 0.1 and 0.3 mg/kg. Other calcium antagonists have been studied in various models of spinal cord injury. They are of particular interest with respect to their effect on posttraumatic SCBF. Nimodipine has been studied most extensively and has been shown to increase SCBF in normal rats and to improve posttraumatic SCBF in rats subjected to clip compression injury. Other investigators have found that neither neurological recovery nor extent of pathological damage was improved with nimodipine. These investigators did not measure SCBF. Verapamil and nicardipine have both failed to improve outcome after weight-drop injuries, but SCBF was not measured.

The results of this study confirm a mild neuroprotective effect of flunarizine in a spinal ischemia model. A significant improvement in hind-limb function at 18 hours after ischemia was followed by a more modest improvement in function at 24 hours. This improvement in neurological recovery was accompanied by a decrement in postischemic SCBF in all but the 1.0-mg/kg treatment group. The optimum dose producing this effect was 0.4 mg/kg. Infarct size was not quantitated in this study, but previous experience with this model
revealed that necrosis is limited to the lumbosacral regions of the spinal cord and involves both gray and white matter changes. Although a single study was unable to demonstrate an effect of flunarizine on SCBF, flunarizine has been demonstrated to augment postischemic cerebral blood flow. This effect was limited to 10 minutes after ischemia and was of doubtful significance regarding outcome. Augmented postischemic SCBF was observed in only the 1.0-mg/kg treatment group and was not correlated with improved survival. This was believed to represent a reperfusion hyperemia similar to that seen in the postischemic spinal cord of baboons pretreated with flunarizine with a 0.2-mg/kg dose. It is not clear why this effect was not seen with lower doses.

Reports in the literature support the observed mismatch between presumed neuronal protection and blood flow improvement. Studies in cerebral ischemia models have demonstrated that flunarizine-treated animals had reduced hippocampal CA1 sector necrosis and improved histological outcome without an increase in cerebral blood flow. This uncoupling of SCBF and neurological recovery suggests that flunarizine is exerting effects through mechanisms other than through direct or receptor-mediated effects on arterial resistance vessels. Calcium is known to accumulate in damaged neurons after ischemic injury. With reperfusion, extracellular Ca²⁺ increases, and cells not initially damaged by the ischemia may be affected by the injurious effects of rapid accumulation of cytosolic calcium. Flunarizine may act to block this deleterious accumulation of cytosolic calcium by damaged neurons. Evidence supporting a direct neuronal action of flunarizine at calcium channels is indirect. Neuronal necrosis was reduced in rat hippocampal CA1 sector when pretreated with flunarizine, although cortex was not protected. Structural neuronal preservation has been correlated with blockade of subcellular Ca²⁺ overload. The overall effect would be an improvement in neuronal cell survival without necessarily affecting vascular reactivity and hence SCBF.

Flunarizine has demonstrated other mechanisms of action that might explain protective effects at the neuronal level. Flunarizine has been shown to inhibit intracellular calmodulin-dependent phosphodiesterase to improve erythrocyte deformability and blood viscosity and to exhibit nonspecific membrane interactions that may help to stabilize damaged membranes. Improved rheology and membrane stabilization may be associated with less edema formation, which might in turn directly impact neuronal viability. Recently, flunarizine was found to enhance neuronal survival of lumbar sensory ganglia after axotomy or nerve growth factor deprivation. The presumed mechanism of action involves an intracellular mechanism distinct from its blockade of receptor-operated calcium channels.

Finally, ischemia is associated with an increase in neurotransmitter activity and an imbalance of excitatory and inhibitory neurotransmitter receptor stimulation, which may play a role in producing ischemic neuronal damage. Flunarizine has been shown to affect the release of certain neurotransmitters in a cerebral hypoxia model. The role these mechanisms might play in ischemia-reperfusion injury of the spinal cord remains uncertain.

In our model of spinal cord ischemic injury, it is clear that flunarizine has the potential to affect many aspects of both cellular calcium and membrane function such that it becomes difficult to postulate a single mechanism of action that would account for the observed improvement in neurological recovery. Our results confirm a failure of flunarizine to improve postischemic SCBF, and thus it is unlikely there are direct vasodilatory effects on spinal cord arterial smooth muscle. Our results indicate that pretreatment with flunarizine leads to improved neurological scores at 18 hours of reperfusion but that the improvement is not sustained at 24 hours. This would suggest that either flunarizine dosing is inadequate and a second dose is needed during the reperfusion period or that the effects of flunarizine are inadequate to compensate for both the initial injury and the consequent generation of free radicals occurring in the reperfusion period.

In this study there was a dose-effect relation between flunarizine treatment and hypotension. Flunarizine does not commonly produce marked decreases in SABP in experimental models. However, in a study of anesthetized rats given flunarizine by either bolus or infusion, investigators were able to demonstrate a transient

<table>
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<th>Table 2. Neurological Recovery Scores at 18 and 24 Hours After Ischemia</th>
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<td>Pretreatment With Flunarizine, mg/kg IV</td>
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<td>2</td>
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<td>Mean±SEM</td>
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*P=.017 compared with untreated group (Mann-Whitney).
†P=.095.
decline in mean arterial pressure from 85 to 69 mm Hg despite an increase in cerebral blood flow and surface Po_{2}.^{37} Other investigators have not seen this hypotenensive effect.^{38} A marked hypotenensive effect could be potentially dangerous in a clinical setting, particularly in the presence of significant cardiac disease. We found that the effect was limited, and normotension was restored in all animals before the induction of ischemia. We were unable to demonstrate that this transient hypotension played a role in determining neurological outcome or SCBF. However, it clearly prolonged the interval between drug administration and the production of ischemia. The effect of this short delay is unlikely to be significant, although we cannot say with certainty that there has been no pharmacologic selection either for or against the higher doses. The mechanism of this hypotension may be that flunarizine is exerting a direct effect on contractile smooth muscle in noncerebral resistance vessels in a time- and dose-dependent fashion. Flunarizine has been shown to increase both muscle and intestinal blood flow, which could lead to peripheral pooling of blood with resultant hypotension on that basis. However, this peripheral vascular effect has been seen with both higher and lower doses of flunarizine.^{39}

It can be concluded from these experiments that flunarizine, a highly lipophilic diphenylalkylamine Ca^{2+} channel antagonist, has mild neuroprotective effects in a rabbit model of ischemic spinal cord injury. The mechanism of protection likely involves inhibition of pathologic cytosolic calcium accumulation or some nonspecific membrane effects of the drug rather than a direct effect on vascular smooth muscle. Significantly, flunarizine has a narrow therapeutic window and can produce transient hypotension when administered at higher doses. These observations indicate that flunarizine or a similar compound may be potentially useful in the prevention of ischemic spinal cord injury such as might occur after aortic reconstructive surgery or direct spinal cord surgery for tumors or vascular malformations.

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References
There is considerable evidence that calcium channel antagonists can produce significant neuroprotection in animal models of cerebral ischemia.\(^1\) However, both experimental and clinical results with various calcium channel antagonists have shown a great degree of variability.\(^1,2\) Because these drugs have both a vascular action (vasodilation) and a direct action on neuronal calcium channels, it is often unclear whether neuroprotection is the result of improved blood flow or reduced calcium overload in neurons. Further complicating the interpretation of experimental results is the fact that vasodilation of resistance arteries leads to systemic hypotension, and there is a large body of evidence indicating that hypotension worsens outcome in cerebral ischemia. Depending on the model, the specific drug, and the route and dose of administration, the balance between the contribution of the many actions of calcium channel antagonists can result in the multiplicity of outcomes seen with this class of compounds.

This well-conducted study evaluates the actions of the dihydropyridine flunarizine in a model of spinal cord ischemia with careful monitoring of both systemic blood pressure and spinal cord blood flow. Flunarizine produced a dose-related reduction in mean arterial blood pressure, but only the highest dose of 1 mg/kg had any significant action on postischemic lumbosacral spinal cord blood flow. Neurological improvement was seen at 0.4 mg/kg, but both lower and higher doses did not produce significant improvement. Since there was no evidence of improved spinal cord blood flow and ischemia was initiated only after the transient hypotension was relieved, these results favor the interpretation that the improvement was the result of a direct action on neuronal calcium channels. However, unlike many of the dihydropyridines, flunarizine can also modulate the action of sodium channels.\(^3\) There is now growing evidence that drugs acting at sodium channels (eg, phenytoin, BW 1003C87) can also produce beneficial effects in models of ischemia.\(^4,5\) Therefore, the improvement found in this study may not be obtained with all calcium channel antagonists.

These results extend the observations in cerebral ischemia to include spinal cord ischemia, which indicate that flunarizine is an effective neuroprotective agent. They also confirm the clinical findings in stroke with calcium channel antagonists, namely, that there is a very narrow therapeutic window that limits clinical utility.\(^2\)

**Peter A. Boxer, PhD, Guest Editor**

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