Intracarotid Etomidate is a Safe Alternative to Sodium Amobarbital for the Wada Test

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Background: The Wada procedure (the intracarotid amobarbital procedure) has been used widely to evaluate the hemispheric dominance of language and memory before temporal lobe surgery in patients with medically refractory seizures. Because of repeated shortage of sodium amobarbital, attempts have been made to find a suitable alternative to sodium amobarbital. The aim of our study was to review our experience with the use of etomidate as an alternative to sodium amobarbital for Wada testing in patients with medically refractory seizures.

Methods: After the ethics approval, we retrospectively reviewed the charts of 29 consecutive patients who underwent Wada test with etomidate. Data from a total of 50 hemispheric injections were reviewed and analyzed. This included the electroencephalographic and motor effects of etomidate injection and their time course (onset and recovery), Wada test results (language laterality and memory performance), and all adverse events during the procedure.

Results: Intracarotid administration of etomidate produced a predictable electroencephalographic and motor effects in all patients. The desirable effect was seen with a single bolus dose of 2 mg followed by an infusion. Shivering was the most common side effect, seen in all the patients. Successful testing was possible in nearly all patients without any major side effects. The “pass rate” of valid tests was in good accord with our previous experience with the use of sodium amobarbital.

Conclusion: From our experience, etomidate is a safe alternative to sodium amobarbital for the Wada test for determining the hemispheric dominance for speech and in predicting the memory outcome.

Key Words: Wada test, sodium amobarbital, intracarotid etomidate injection, EEG and motor effects, language and speech lateralization

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The Wada procedure, also known as the intracarotid amobarbital procedure (IAP), has been used for >50 years to evaluate language laterality and to predict the postoperative memory outcome in the surgical planning of patients with medically refractory temporal lobe epilepsy.1,2 The basic methodology of IAP is to inject a short-acting intravenous (IV) anesthetic agent into the carotid artery to anesthetize ipsilateral hemisphere, allowing one to assess the language and memory functions of the contralateral hemisphere in isolation. Sodium amobarbital has been the standard drug used for IAP for >50 years.1,2 In most centers, anesthesiologists were not usually present during this procedure and the radiologist usually injected the sodium amobarbital. Because of frequent interruptions with the supply and limited availability of sodium amobarbital, various anesthetic agents have been tried for this procedure, and hence, anesthesiologists are now being involved in this procedure.3-9 The use of etomidate in IAP was developed by the Epilepsy Surgical Program at the Montreal Neurological Institute, in which it was reported to be an effective alternative to sodium amobarbital, referring to the procedure as the etomidate speech and memory (eSAM) test.9 Intracarotid administration of anesthetic agents poses unique pharmacokinetic challenges for anesthesiologists. The purpose of this study was to review our experience with the use of etomidate as an alternative to sodium amobarbital for Wada testing in patients with medically refractory epilepsy.

METHODS

Subjects

After the institutional research and ethics board approval, we retrospectively reviewed the clinical, electroencephalographic (EEG), and neuropsychological data of

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29 consecutive patients (one of whom underwent 2 procedures) who underwent eSAM in our institution from January 2007 to December 2011. All patients in our institution undergo extensive presurgical evaluation, consisting of noninvasive and invasive investigations (where required) before the surgical treatment for their medically refractory epilepsy. Language dominance is usually determined by functional magnetic resonance imaging (fMRI). Generally, patients who are deemed to be at risk of drastic postoperative memory dysfunction are referred for IAP.

Procedure

The procedures were performed in the neuro-radiology suite. Patients were monitored with electrocardiography, noninvasive blood pressure monitoring, and pulse oximetry. All patients had continuous monitoring of 24-channel EEG. An anesthesiologist administered the drug and monitored the patient. A neuropsychologist performed the motor, language, and memory assessments during the procedure.

Under local anesthesia, the femoral artery was cannulated using a 5-F catheter with a dead space of 1.2 mL. The catheter was advanced into the internal carotid artery until the tip of the catheter was at the level of the first cervical (C1) vertebral body. A cerebral angiogram was performed to confirm the absence of any significant cerebral cross-flow or abnormal vascular circulation. In all except 1 case, the first injection was administered in the hemisphere with the seizure focus to test the contralateral hemisphere, thus mimicking surgery. Before the injection, patients were presented with 5 pictures of objects that they were to remember. Etomidate 2 mg (2 mg/mL) was injected as a bolus over 30 seconds using a syringe driver infusion pump (Medfusion 3500; Smith Medical MD Inc., St. Paul, Minnesota) followed by an infusion of 6 mL/h (12 mg/h) etomidate. After the onset of contralateral hemiplegia, adequate contact with the patient was verified by the execution of a simple verbal command or by observing the patient’s visually orienting or tracking stimuli. Then, all the memory items (10 common objects that were to be named) were shown. The infusion was then stopped and from this point forward, language (reading, naming, repetition, spelling, and counting) and motor functions were sampled repeatedly. Once the patient recovered from the drug effect, both clinically and electrophysiologically, a yes-no recognition memory test was performed, which consisted of the presentation of the 10 old objects and 10 new (distractor) objects. Patients were also tested with the preinjection 5 items to ensure that the testing was valid. Memory was considered adequate (pass) when ≥70% of the objects shown during the drug effect were recognized and 90% of the distractors were rejected. If indicated, the second test was then performed in a similar manner on the other side.

Data Analysis

Data from a total of 50 hemispheric injections were reviewed and analyzed. This included the EEG and motor effects of etomidate injection and their time course (onset and recovery), eSAM test results (language laterality and memory performance), and all complications during the procedure. Analysis of EEG changes included the time of onset and recovery of slow wave activity in response to etomidate infusion, the presence of sharp wave activity, and the contralateral spread of the slow wave activity. A descriptive statistical analysis was performed using the Statistical Package for the Social Sciences version 20. All values are expressed as mean ± SD.

RESULTS

A total of 29 patients underwent 50 hemispheric injections. The demographic data are as shown in Table 1. All patients received a 2-mg bolus of etomidate followed by the infusion of 12 mg/h. The average duration of infusion was 3 minutes 26 seconds (range from 2 min 46 s to 3 min 56 s) with a mean dose of 2.68 mg (dose range from 2.55 to 2.78 mg). Sixteen patients also had an injection of the contralateral hemisphere (bilateral injection) to test the functional adequacy of the to-be-resected temporal lobe. In 4 patients, the test was repeated on the same side to confirm the validity of the first test because of initial poor contact with the patient, strong emotional reaction preventing full engagement, failure of the preinjection items, and an unusual delayed effect of etomidate. In patients who had bilateral injections (n = 16), the average time between the first and the second injections was 26 ± 7 minutes.

EEG Effects After Etomidate Injection

Immediately after the injection of etomidate, all patients showed EEG slowing with delta and/or theta waves on the ipsilateral side. The onset of EEG slowing was at 29.46 ± 12.69 seconds after the bolus, and the recovery to baseline was 374.26 ± 170.19 seconds after stopping the infusion. Contralateral hemispheric EEG slowing was also noticed in 9 patients. This slowing was observed mainly in the frontal areas (n = 9) and in some patients (n = 5) in the parasagittal and temporal areas. After the second injection, the onset of EEG effect was earlier (24.2 ± 8.73 s) and the recovery was delayed (454.90 ± 184.39 s) compared with the first injection (Figs. 1, 2). This was not statistically significant.

Intracarotid injection of etomidate produced an increase in the interictal epileptiform activity in 70% of all the injections (35/50). This increased interictal spikes appeared almost immediately after etomidate injection and was simultaneous with the EEG slowing. In all patients, interictal spiking was seen only after ipsilateral

<table>
<thead>
<tr>
<th>TABLE 1. Demographics</th>
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<tbody>
<tr>
<td>Total no. patients/hemispheric injections</td>
</tr>
<tr>
<td>Age (y) (mean ± SD)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Diagnosis (TLE:brain tumor)</td>
</tr>
<tr>
<td>Handedness (right:left)</td>
</tr>
<tr>
<td>Hemispheric dominance (left:right)</td>
</tr>
<tr>
<td>Epileptic side (left:right)</td>
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<tr>
<td>Injection (unilateral/bilateral)</td>
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TLE indicates temporal lobe epilepsy.
injection to the epileptogenic side, except in 1 patient who had bilateral interictal epileptiform activity after unilateral injection.

Motor Effects After Etomidate Injection
All patients had contralateral hemiplegia after injection. The onset of motor and EEG effects occurred simultaneously, but the recovery times were different (Figs. 1, 2). The onset of motor effect was seen at 29.7 ± 15.4 seconds after the bolus and the recovery to grade 5 power was seen 558 ± 208 seconds after stopping the infusion. The onset (26.75 ± 10.46 s) and recovery (543 ± 188 s) of the motor effect was earlier after the second injection compared with that of the first injection. This was not statistically significant.

FIGURE 1. The onset time [mean ± SD (s)] of electroencephalographic (EEG) and motor effects after the first and the second injections.

Neuropsychological Assessment
Neuropsychological assessments were considered to be valid in 44 (88%) injections. They were considered to be invalid in 6 injections (5 patients) because of vomiting (n = 1), bilateral EEG effects and poor contact (n = 2, but in the same patient), failure to recognize preinjection items (n = 1), adverse emotional reaction (n = 1), and delayed effect of etomidate (n = 1). In 4 patients, the test was repeated and valid data were obtained.

Language
Language dominance had been established previously in most patients using fMRI: 25 were left dominant, 2 were right dominant, and 2 were unable to complete the fMRI paradigms. The eSAM test results were concordant with fMRI data. Speech arrest followed

FIGURE 2. The recovery time [mean ± SD (s)] of electroencephalographic (EEG) and motor effects after the first and the second injections.
injection in the dominant hemisphere in 14 patients, with full recovery of language by 438 ± 138 seconds (range 238 to 660 s).

Memory and Outcome

In our study, 24 patients passed the test and 5 failed the test. Currently, 19 patients have undergone standard temporal lobe resections. Of 19 patients, 14 have undergone a 1-year postoperative neuropsychological testing (dominant hemisphere resection, n = 8; nondominant, n = 6). None of the patients developed a severe postoperative memory deficit or speech disturbance.

Adverse Events

No hemodynamic changes were noted with the intracarotid administration of etomidate except in 1 patient. This patient had significant nausea and vomiting immediately after the injection of etomidate accompanied by tachycardia (110 beats/min) and hypertension (140/90 mm Hg) that lasted for 3 minutes. This episode was attributed to a possible electrographic seizure and he could not complete the test on that day. He successfully completed the test on another day under antiemetic prophylaxis with 2 mg IV granisetron. Shivering was the most common side effect and was seen in all patients. In 50% of the patients, the shivering was severe, but oxygen saturation was maintained (> 94%) in all patients without supplemental oxygen. In contrast to myoclonic jerks, shivering involved predominantly the extremities and was self-limiting, lasting only for a few minutes.

Mood changes were seen in 23% of the patients and consisted of both positive and negative mood experience. In 3 patients, these were quite extreme, involving agitation and/or sobbing that occurred rather late in the procedure; 2 patients required small doses (20 mg) of IV propofol to sedate them.

DISCUSSION

Fifty years ago, Wada1 first introduced the concept of intracarotid sodium amytal injection for the purpose of speech lateralization. Since then, numerous efforts have been made to identify a minimally invasive method for determining language and memory dominance without sacrificing accuracy.10 For language testing, iMRI has been shown to identify language dominance with 95% accuracy.10 Therefore, the use of the Wada procedure for the sole purpose of language lateralization is seldom justified. The postoperative memory outcome can be predicted by standardized neuropsychological testing in most patients with unilateral temporal lobe epilepsy.11 However, there is no alternative to the Wada procedure to assess the risk of severe postoperative memory loss in individuals with evidence of bitemporal disease or dysfunction.

Etomidate, an imidazole derivative, is a potent nonbarbiturate hypnotic agent with no analgesic properties.12 Its anesthetic effects are mediated through the modulation of γ-amino butyric acid (GABA) A receptors.12 It has a rapid onset (30 to 60 s) and a short duration of action (5 to 10 min) with minimal hemodynamic effects. In our study, intracarotid administration of etomidate produced predictable EEG and motor effects (ipsilateral EEG slowing, contralateral hemiplegia) in all patients. The desirable effects were seen with a single bolus dose of 2 mg followed by an infusion. Successful testing was possible in nearly all patients without any major side effects. The “pass rate” of valid tests was in good accord with our previous experience with the use of sodium amobarbital. Our findings are also in agreement with those of Jones-Gotman et al10 who pioneered the use of etomidate for IAP.

Intracarotid administration of anesthetic agents has a different pharmacokinetic profile compared with the IV route.13 The ideal pharmacokinetic properties of the drug used for the Wada test should have a short duration of action (around 15 min) to allow adequate time for language and memory testing without multiple dosing. It should also have very minimal residual effect on consciousness to allow multiple tests in a single session. Finally, it should produce consistent effects both clinically and electrophysiologically without any epileptogenic properties or other side effects. Sodium amobarbital was the standard drug used in the Wada test for many decades because of its short duration of action and low toxicity, as well as clinicians’ extensive experience with its drug effects. Recently, the supply of sodium amobarbital has been disrupted worldwide and has led to exploration of other possible agents. Pentobarbital, methohexitol, secobarbital, etomidate, and propofol have all been investigated as substitutes.3-9 The summary of anesthetic agents used for the Wada procedure is shown in Table 2.

The use of propofol as an alternative to sodium amobarbital has been studied extensively. However, the incidence of adverse reactions reported in the literature were very high with propofol, most patients experiencing significant eye pain, facial and ocular flushing, tonic posturing, and conjugate eye deviation.

The intracarotid administration of drugs has unique pharmacokinetic challenges. All the drugs used for intracarotid injection have been administered as single or multiple boluses by hand injection. The intra-arterial dose of anesthetic agents is 1/10th of the IV dose,13 and this usually does not vary with the patient’s weight. The volume of the drug used for injection varies from 3 mL (sodium amobarbital) to 10 mL (pentobarbital). Etomidate is very unique in that the intra-arterial dose is 2 mg or 1 mL of the standard concentration, and in our experience, any dilution of the drug failed to produce the desired clinical effects. As the intra-arterial dose of etomidate is 1 mL (2 mg), flushing the catheter dead space after the bolus will dilute the drug and abolish the clinical effects. Hence, etomidate needs to be injected undiluted as a 1 mL (2 mg) bolus using an infusion pump followed by a maintenance infusion to prevent the dilution of the drug from the flushing of the angiographic catheter.

The clinical and EEG effects of intracarotid etomidate were comparable to those of sodium amobarbital. The onset of EEG and motor effects after etomidate injection occurred
TABLE 2. Summary of Anesthetic Agents Used for the Wada Test

<table>
<thead>
<tr>
<th>Agent (Concentration)</th>
<th>Dose</th>
<th>Comments</th>
<th>References</th>
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<tbody>
<tr>
<td>Amobarbital (25 mg/mL)</td>
<td>75-125 mg followed by 25 mg</td>
<td>Gold standard. Short duration of action, low toxicity, extensive clinical experience</td>
<td>Wada and colleagues&lt;sup&gt;1–4,14&lt;/sup&gt;</td>
</tr>
<tr>
<td>Methohexital (1 mg/mL)</td>
<td>3 mg followed by 2 mg</td>
<td>Fluctuating levels of drug effect—reliability of the test questionable. Electroencephalographic changes are brief and less obvious—the drug effect is monitored by clinical means (motor and speech)</td>
<td>Buchtel, Andelman, Loddenkemper and colleagues&lt;sup&gt;6,7,14–16&lt;/sup&gt;</td>
</tr>
<tr>
<td>Propofol (1 mg/mL)</td>
<td>10-20 mg followed by 10 mg</td>
<td>Short duration of action—need for multiple boluses</td>
<td>Mikati, Takayama and colleagues&lt;sup&gt;4,6,17&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pentobarbital (2 mg/mL)</td>
<td>20-24 mg followed by 12-16 mg</td>
<td>Very long duration of action</td>
<td>Kim and colleagues&lt;sup&gt;3,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Secobarbital (5 mg/mL)</td>
<td>10-25 mg</td>
<td>Effects similar to amobarbital with minimal side effects</td>
<td>Yamaguchi et al&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Etomidate (2 mg/mL)</td>
<td>2 mg bolus followed by 12 mg/h</td>
<td>Effects similar to amobarbital</td>
<td>Jones-Gotman and colleagues&lt;sup&gt;6,9&lt;/sup&gt;</td>
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Simultaneously. The onset of EEG slowing was earlier and recovery was delayed after the second-side injection (on the nonepileptogenic side) compared with the epileptogenic side (first-side injection). This difference may be due to the variation in distribution of GABA and benzodiazepine receptors in the epileptogenic and nonepileptogenic cortex.<sup>18</sup> It has been shown that there is a reduction in the number of these receptors in the epileptogenic area of patients with temporal lobe epilepsy.<sup>19–21</sup> As etomidate acts on GABA receptors, delayed onset and early recovery after injecting into the epileptogenic side may be due to the decreased number and affinity of GABA receptors on this hemisphere compared with the normal nonepileptogenic side.

In the seminal study by Jones-Gotman and colleagues, the contralateral (second) injection was carried out on a separate day to avoid potential interactions with the first injection.<sup>9</sup> However, in addition to the time and cost, each procedure of transfemoral cerebral angiography carries a risk of stroke and other morbidity.<sup>22</sup> Thus, our decision was to perform both hemispheric injections at the same setting. With sodium amobarbital, it has been recommended to wait for 45 minutes between injections. In our study, the average time between the first and second injection was 25 minutes (range, 13 to 39 min).

Shivering was the most common side effect seen during this procedure. It has also been reported with other anesthetic agents. One study quotes 46% incidence of transient shivering with amobarbital.<sup>23</sup> The exact mechanism of shivering is not known. One of the postulated mechanisms was that shivering may be caused by the injection of cold drug into the brain, activating cold responses from the hypothalamus. Because of this, in some centers, sodium amytal was prewarmed routinely before injection. However, Shah et al<sup>23</sup> have reported that shivering was more likely to follow sodium amobarbital injection if there was no filling of the posterior circulation on a cerebral angiogram. They postulated that a transient but selective functional lesion of the anterior hypothalamus produced by the effects of sodium amobarbital may result in disinhibition of the posterior hypothalamus and other brainstem thermoregulatory centers, thereby inducing transient shivering.<sup>23</sup>

Transient mood changes were observed infrequently during the procedure. In our study, 3 patients became very restless and agitated, especially after the second injection, needing sedation to calm them; several others showed less drastic effects involving sobbing or laughter. Etomidate can cause activation of interictal epileptiform activity and also electrographic or clinical seizures.<sup>24,25</sup> In our study, increased interictal activity was seen in 28 injections, but there were no clinical seizures. Adrenal suppression has been reported even with a single dose of etomidate injection.<sup>26,27</sup> However, this was in settings where the etomidate dose was 10 times that used in the eSAM test.

Although the outcome data from postoperative neuropsychological testing are based on only half of the patients who underwent eSAM, it is important to note that the test validity appears good. That is, none of the patients developed a severe postoperative memory deficit (thus excellent specificity) and those who did poorly on
the contralateral injection showed less change after the surgery (therefore good sensitivity).

CONCLUSIONS

From our experience, etomidate is a safe alternative to sodium amobarbital for the Wada test for determining the hemispheric dominance for speech and in predicting the memory outcome. Intracarotid administration of etomidate produced predictable EEG and motor effects (ipsilateral EEG slowing, contralateral hemiplegia) in all patients. Successful testing was possible in nearly all the patients without any major side effects. The “pass rate” of valid tests was in good accord with our previous experience with the use of sodium amobarbital.

REFERENCES