Etomidate speech and memory test (*e*SAM)

A new drug and improved intracarotid procedure

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Abstract—*Background:* The intracarotid amobarbital procedure (IAP) is an important part of comprehensive investigation of patients who are candidates for surgical treatment of epilepsy. Owing to repeated and lengthy shortages of amobarbital, causing delays in elective surgery, attempts have been made to find a suitable alternative anesthetic. The authors report their experience using etomidate, a widely used agent for the induction of anesthesia. *Methods:* Sixteen consecutive patients requiring IAP to evaluate memory or to lateralize speech underwent the procedure using etomidate. Prior to the procedure a catheter was placed in the internal carotid artery and an angiogram was performed. EEG was recorded and read online by an electroencephalographer. An anesthetist injected the drug, administered by bolus followed by an infusion, which was maintained until each speech measure had been sampled and new memory items had been introduced. The infusion was then stopped and testing continued as in a standard IAP. *Results:* In all cases (30 hemispheres) contralateral hemiplegia followed injection. EEG slow waves were observed in every injected hemisphere, with some contralateral slowing anteriorly in 18. Global aphasia with preserved attention and cooperation followed dominant-hemisphere injections. These phenomena remained during infusion, and upon its termination returned gradually to baseline over a period of about 4 minutes. *Conclusions:* Etomidate is a viable alternative to amobarbital, and its administration by bolus followed by infusion offers an improvement over the traditional intracarotid amobarbital procedure. Cognitive tests can be performed during an assured hemianesthesia of the injected hemisphere.

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For more than 45 years the intracarotid amobarbital procedure (IAP) has been used to lateralize cerebral dominance for speech[1-3] and to evaluate memory in each hemisphere independently.[4] Little of the original IAP methodology has changed over the years. Details such as specific tasks administered or dosage differ from center to center,[5] but the basic methodology, consisting of injection of a barbiturate for brief anesthetization of one hemisphere and administration of simple speech and memory tests, does not. The effect of the drug is usually completely dissipated after about 6 to 8 minutes,[6,7] and the full effect lasts only about 3 minutes, depending on injection parameters.[8,9]

The drug used originally for this procedure and still used the most frequently is sodium amobarbital. Owing to repeated and often lengthy shortages, attempts have been made to find a different anesthetic agent. Methohexital (Brevital) has been used with some success[10-12] and propofol has been tried.[13-15] Methohexital is also not readily available and is so short-lived that reinjection is usually required.[12] Propofol, which is contained in an oil-in-water-emulsion, has been proposed as an alternative but is not an ideal choice because of the lipid carrier.[16,17]

We report our experience using etomidate, a widely used agent for the induction of anesthesia.[18-20] In addition to introducing this new anesthetic agent for the IAP, we made an important change in the basic procedure: after the initial bolus has been injected, an infusion is maintained until the critical speech and memory tests have been administered.

Methods. *Subjects.* The subjects were patients requiring an IAP for evaluation of memory, or for speech lateralization, or both, prior to surgery. Sixteen patients (seven women) have been tested. With rare exceptions we test both cerebral hemispheres; in this sample two patients received only one test, resulting in a total of 30 injected hemispheres. Seven subjects received the test for determination of hemispheric dominance for language, four for memory evaluation because bitemporal dysfunction was suspected, and five for both reasons. However, the procedure was exactly the same for all clinical indications. All patients were candidates for epilepsy surgery except one, tested for speech dominance, who had a right frontal-lobe tumor and no epilepsy. In subjects with epilepsy, the focus was on the left side in six and on the right in five, while four had bitemporal epileptic abnormalities without clear

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Table 1 *Subjects (n = 16)*

Abnormal side	N		Sex		Mean age, y (range)	Mean FSIQ (range)	Handedness			Reason for test		Speech dominance†		
							No. per category							
	Patients	Injections*	F	M			L	R	S	M	B	L	R	BL
Left	6	11	1	5	35.3 (16–46)	93.2 (83–101)	2	4	2	3	1	4	2	0
Right	6	9	4	2	37.7 (26–47)	90.3 (76–113)	4	2	5	0	1	4	1	1
Bilateral	4	6	2	2	36.5 (28–48)	90.8 (72–112)	2	2	0	1	3	3	1	0

* L, one patient tested one side only; R, one patient excluded, one tested one side only; BL (bilateral), one patient tested one side only and excluded.

† As determined by etomidate speech and memory test (*e*SAM).

S = determine hemispheric dominance; M = evaluate memory; B = both; BL = bilateral.

lateralization. The patients with bitemporal epilepsy underwent implanted electrode (SEEG) studies; two had the etomidate procedure after the SEEG study was completed, and two were implanted at the time of the procedure. Four tests were excluded from group results (but will be discussed separately), resulting in 26 injections—13 left, 13 right—reported in the group data. Demographic data are shown in table 1.

Etomidate: Characteristics of the drug and injection parameters. Etomidate (R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate) is an imidazole derivative and a potent nonbarbiturate hypnotic agent with no analgesic properties.[18,19] It has a rapid onset and short duration of action and minimal hemodynamic effects; it is considered safe and effective in its common IV use in operating rooms, intensive care units, and emergency departments.[20-22] Etomidate may, however, cause myoclonus, tremor, and dystonic posturing in 86.6% of patients, most often at the beginning of deep anesthesia.[23] Etomidate may increase spike activity in patients with epilepsy,[24,25] and, in isolated cases, elicits seizures or epileptiform activity in persons without epilepsy.[25-27] Finally, etomidate has a dose-dependent and cumulative suppressive effect on adrenal function.[21,28] A single dose of the drug blunts the adrenocortical axis for up to 24 hours. This effect, however, appears to be clinically relevant only in critically ill patients.

In our procedure, a 2 mg initial bolus of etomidate (0.03–0.04 mg/kg) is injected in the internal carotid by an anesthetist. This concentration was determined using an algorithm that would reproduce local plasma levels identical to those achieved by a usual IV systemic dose (0.3 mg/kg over 30 to 60 seconds). The bolus is injected by infusion pump and is followed by an infusion (0.003–0.004 mg/kg/minute) at a rate of 6 mL per hour.

Procedure. General procedure. As with our amobarbital procedure, patients practiced the day before testing the first hemisphere. The speech and memory tasks were the same on all three tests (the practice, and the test for each hemisphere), but the specific materials used—words, objects, sentences—were different.[29] There was no injection during the practice.

During the procedure proper, a catheter was inserted by a neuroradiologist in the internal carotid artery and an angiogram was performed. EEG was recorded and read online by an electroencephalographer. Before injection, a baseline was obtained for EEG, visual fields, hand strength, and finger mobility measures, and for the cognitive tests. After the initial bolus, an infusion was maintained with an infusion pump until all speech tests had been sampled and critical memory items had been presented (see below). After the infusion, testing continued until all speech tests were completed and baseline levels were observed on EEG, hand strength, and language (in dominant hemisphere injections). At that point, a recognition memory test was given and the patient's subjective comments were obtained.

EEG. The EEG recording started several minutes before the bolus injection and was continued for several minutes after all clinical and EEG signs had returned to baseline. Twenty-five channels were recorded, including the 19 standard scalp electrodes and inferior temporal electrodes (F9, T9, P9 and F10, T10, P10), referenced to CPz. In two patients, the EEG was recorded from multi-contact depth electrodes placed bilaterally in the temporal lobes, recording from the amygdala, hippocampus, and temporal neocortex, and from epidural electrodes placed over the first temporal convolution. The EEG was sampled at 200 Hz, with a low pass filter at 65 Hz. The scalp EEG was displayed in a bipolar antero-posterior montage. After the injection, a section of the baseline tracing was always retained on the screen to facilitate comparison of the ongoing EEG with the baseline. EEGs were subsequently reviewed to mark the time of onset of EEG changes, their pattern and spatial extent, and the time of return to baseline.

Cognitive tests. Testing proceeds in three stages: at baseline, during the drug effect, and after the effects of the drug have dissipated (post-drug stage). We test speech for comprehension, naming, sequential speech (counting, reciting the days of the week forward and backward), spelling, reading, and repetition of words and sentences.[29] These different tasks are given in blocks during baseline testing, but after injection we cycle through them, giving two items per task so that all are sampled, after which new memory items are presented and the infusion is stopped. Speech testing is then completed after termination of the infusion.

Twenty-four real objects are used to test memory: eight are presented before injection to provide a baseline and a comparison with eight new "critical" items to be presented during the drug effect. The remaining eight items are novel objects included as foils during final memory testing, which is carried out in the post-drug stage. Thus all 24 objects are shown during a final yes-no recognition memory test.

Figure 1 shows the time line for injection, infusion, and presentation of cognitive tests. A similar time line for a typical IAP is also shown, for comparison.

Results. *Neurologic findings during drug effect.* Before and during injection patients raised both arms, wiggled their fingers, and counted. A lag of approximately 40 seconds elapsed between initiation of the injection and appearance of the first clinical signs of hemianesthesia. These signs included the appearance of slow waves in the EEG, slowing and then stopping of contralateral finger movements (after which that arm fell), and slowing and slurring of speech (figure 2). In all cases the contralateral arm fell slowly following injection, and a contralateral hemiplegia was observed. Dysarthria was noted soon after injection in 11 of the 13 nondominant hemisphere injections and in 3 of 13 dominant hemisphere injections. Speech was disrupted in the 13 tests that were then designated dominant hemisphere injections. A contralateral facial weakness was seen in 73% of tests and a contralateral visual field defect in 50%. After stopping the infusion these effects waned over a period of just over 4 minutes on average, until baseline was reached. Average duration of injection, time to first signs of effect, duration of infusion, and

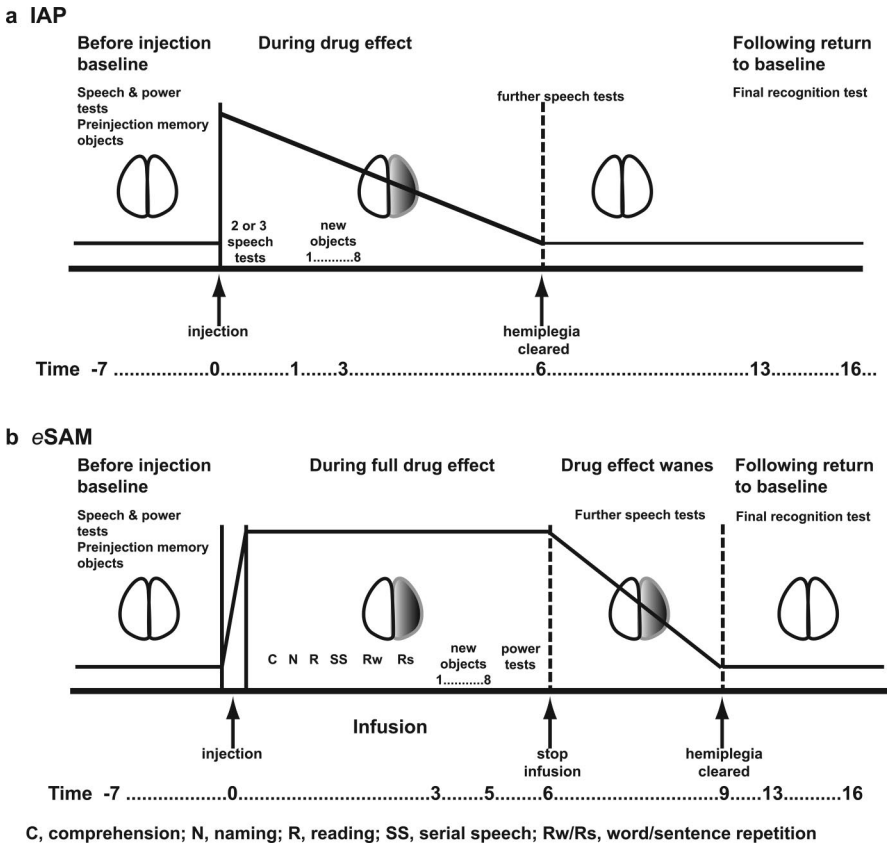

Figure 1. Intracarotid anesthetic procedures: time course of events in the intracarotid amobarbital procedure (IAP, A) and in the etomidate speech and memory test (eSAM, B). Solid vertical lines signify moment of injection; this line is doubled in B, indicating the 40-second lag between bolus injection and initiation of drug effect in the eSAM procedure. Downward sloping line indicates waning of the drug effect; this begins soon after injection with amobarbital and begins after infusion has stopped with etomidate. Fully white brain cartoons signify bilateral baseline function; half black brain cartoons signify hemianesthesia or only one hemisphere fully functional.

time to recovery after cessation of infusion for measures of language and physical signs are shown in table 2.

EEG. In one study the EEG was lost and in another the recording started after the injection. We therefore analyzed 24 injections (20 with scalp EEG and 4 with SEEG). Drug-induced changes in the EEG occurred on average 39 seconds after initiation of injection and always occurred within a few seconds of the first clinical signs. The changes were generally consistent with those observed in the IAP in scalp and intracerebral recordings.[6,30-32] In the scalp EEG, they consisted of slow waves in the delta range sometimes mixed with theta frequencies (figure 3). The slow wave activity predominated on the hemisphere of injection but was also visible in the contralateral frontal region in 18 injections. In two injections, the slow activity was almost symmetric in the two hemispheres, despite clear lateralized clinical manifestations. In one injection, the slow waves appeared as usual but disappeared after 41 seconds, then returned 153 seconds later and continued as in other injections. The clinical signs of hemianesthesia continued uninterrupted during this EEG fluctuation. In the SEEG recordings (example, figure 4), drug-related changes were limited to the hemisphere of injection. In all four injections there was a large increase in slow waves in all regions of the temporal lobe.

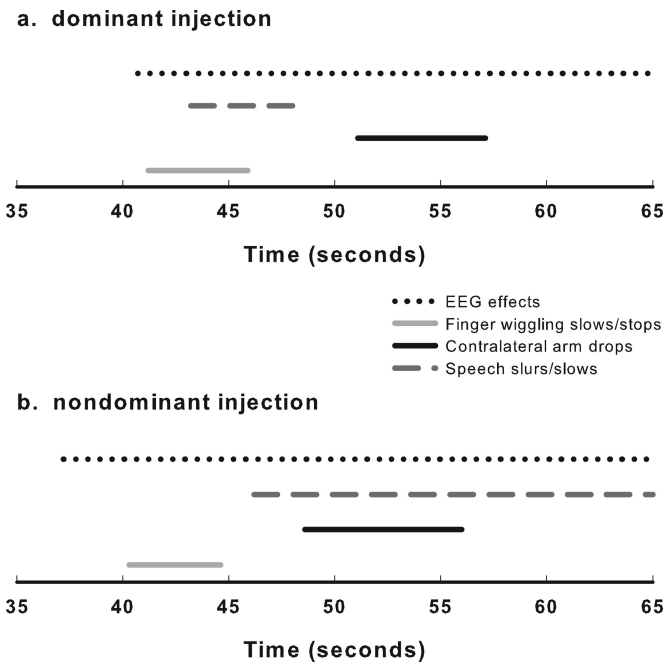

Figure 2. Time of occurrence of first drug effects after injection of etomidate, separately for dominant vs nondominant injection.

Slow waves decreased and stopped on average 4 minutes 13 seconds after the end of the infusion, corresponding closely to the end of behavioral signs of hemianesthesia (compare table 2 to table 3). Similarly to the IAP, it was generally difficult to mark the end of slow wave activity because of the gradual change. Unlike for the IAP, however, we did not see intermittent slow waves in this period (table 3).

Interictal spike activity was activated or induced in eight injections: four during scalp EEG (three patients) and four during SEEG recordings (two patients). The increased spiking appeared almost simultaneously with the slow waves and always stopped before (mean slow wave duration vs increased spiking, 10 minutes 17 seconds vs 6

Table 2 *Time course of injection (n = 26) and drug effects*

Side of injection	No. of injections	Mean duration of injection, sec	First clinical sign of effect, sec	Mean duration of infusion, min, sec	Mean time to recovery after infusion stopped, min, sec	
					Contralateral arm	Speech
Dominant	13	64.6	41.2	5, 42	4, 09	4, 59
Nondominant	13	64.8	40.3	6, 23	4, 05	—

minutes 15 seconds). In three injections with scalp EEG, spike activity was increased on the injection side and ipsilaterally to the known epileptic focus, while the fourth injection resulted in the appearance of a continuous 2.5 spike-and-wave activity also on the injection side, but this time in the nonepileptic healthy hemisphere.

In the SEEG recordings, etomidate caused a clear increase in the rate of interictal spiking in the ipsilateral limbic structures, except in one injection where the activity took the form of periodic spiking, particularly in the temporal neocortex.

Language. Etomidate injection resulted in a global aphasia with preserved attention and cooperation in 13 tests, thus demonstrating that the injected hemisphere was dominant for language. Performance on all language tasks was disturbed during the infusion. For the production tasks, one patient produced unintelligible mumbling and one repeated a stereotyped word not appropriate to the task. Our first patient, whose dose was too low and whose results are therefore not included in group data, did not produce meaningful speech but counted in a stereotyped way for about 2 minutes after injection. Complete speech arrest throughout the period of infusion was observed in the remaining patients. After all language tasks had been sampled and the new memory items shown, the infusion was stopped and cycling through language tasks continued until all were performed at baseline levels. Because the return of speech to baseline occurred gradually, the language tests sampled speech as the aphasia cleared, passing through a stage of dysphasia and then recovery.

Memory. On average, presentation of the critical memory items during the drug stage began 3 and one quarter minutes after injection and lasted for just under 2 minutes. Recognition testing for the baseline objects and the critical drug-stage objects was started on average 13 minutes after injection, which was in all cases after the drug effect had dissipated completely as determined by return of motor function, EEG, and, for dominant-hemisphere injections, speech to baseline levels. Memory was considered adequate when 65% or more of the drug-stage objects were recognized (false positive errors and failing to recognize baseline objects are rare). Table 4 shows the memory outcome for three categories—memory tests passed or failed or borderline—separately for injection ipsilateral and contralateral to the seizure focus. The table also shows the percent of cases who in final questioning reported awareness of power loss, as memory for events of the test have been considered to be additional, informal, memory results by some.[33] Two patients with bitemporal epilepsy who did not have operations are shown separately; one of these was found to have greater epileptic abnormality on the right side, but a more abnormal side could not be determined for the other one.

Mood and insight. We examined mood changes after injection of etomidate. Change from baseline was observed in 6 of 13 injections into the dominant hemisphere and 3 of 13 nondominant injections. Independent of the question of

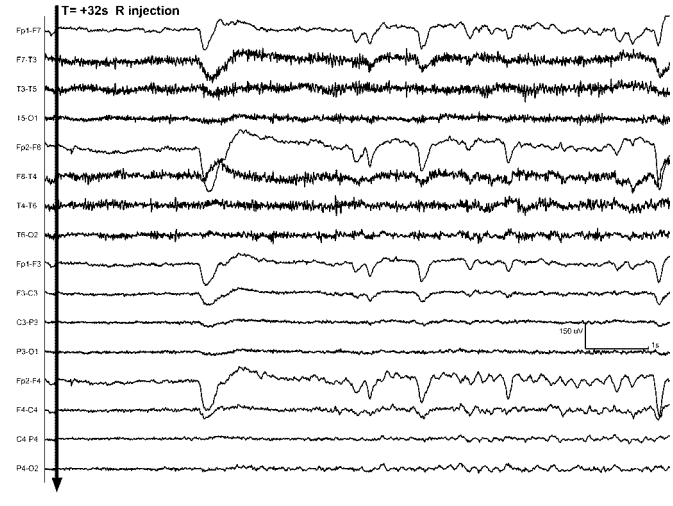

Figure 3. Sample of scalp EEG recording made during eSAM testing.

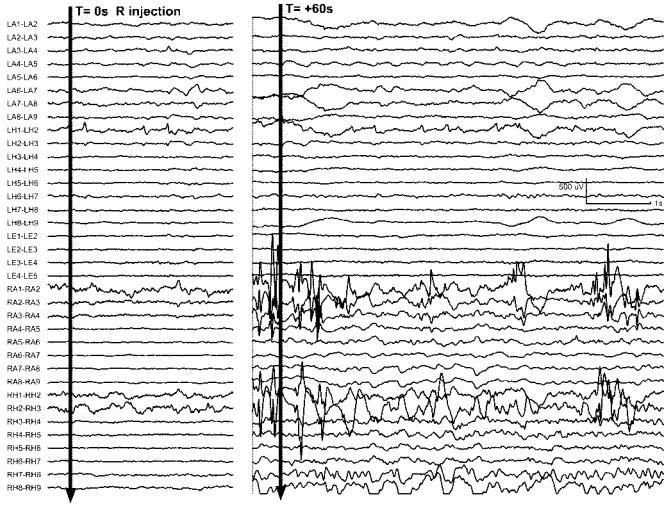

Figure 4. Sample of EEG recorded from depth electrodes implanted in temporal lobes during the eSAM procedure. Multicontact depth electrodes are inserted laterally. Electrodes LA and RA are aimed at the amygdala, contact 1 being the deepest and contacts 4 to 9 being in the neocortex. LH and RH are aimed at the hippocampus. LE electrodes are placed epidurally over the first temporal convolution.

Table 3 *Time course of ipsilateral EEG (n = 24) slow waves*

Side of injection	No. of injections	First EEG change, sec	Mean time to baseline recovery after infusion stopped, min, sec
Dominant	12	40.7	4, 18
Nondominant	12	36.8	4, 09

change, we noted the overall valence of mood during the test and classified emotional expression during the drug effect as positive, negative, flat, or labile. When noticeable emotional expressions occurred, they were more often after injection into the dominant hemisphere (9 of 13 dominant injections, 4 of 13 nondominant). Mood was almost exclusively positive (6 dominant, 3 nondominant), with one instance of negative affect, one of flat, and one that was positive followed by flat. One patient showed a labile mood, switching rapidly between apparently laughing and apparently crying, with the actual mood being difficult to decipher (dominant hemisphere injection).

Patients showed a relatively high incidence of insight into injection-induced changes. Eight of 13 patients recalled language disturbance after dominant hemisphere injection: four had full awareness of their speech loss, whereas the others recalled disruption of speech production but not of comprehension. Eight patients recalled contralateral weakness after dominant, and five after nondominant hemisphere injection. Two patients described a visual field defect after dominant, and none after nondominant, hemisphere injection. It is often difficult to establish the objective presence of a visual field defect during the drug effect, but we had clear evidence of such defect after dominant hemisphere injection in seven, and after nondominant injection in six patients.

Side effects. In nine patients (12 tests, or 46% of the 26 injections) a shivering-like tremor occurred during the infusion, almost always involving the upper extremities (the hand and arm). This occurred on the hand contralateral to injection, although in 7 of the 12 injections it affected the ipsilateral hand also. The tremor never occurred on the ipsilateral side alone. When it did occur it was usually mild—in 58% it was very mild or almost imperceptible—the rest were mild trembling except for two cases that could be characterized as moderate shaking. In some, the tremor appeared only while the patient manipulated objects, and in some it resembled the shivering (as though cold) that is seen also in some patients after amobarbital injection. Most patients did not react to this tremor during the test, and only three recalled it when questioned at the end of the procedure. Interestingly, the EEG recording showed no concomitant epileptiform abnormalities except in two injections (both in the same bitemporal patient, tested during his SEEG investigation): spiking was increased during the right side infusion in the limbic structures only, and was limbic and neocortical during the left side infusion.

Physical sequelae to the procedure. Two to 3 hours after each procedure, patients were questioned explicitly about possible pain, headache, or other complaints related to the test. Patients were found in good spirits after their tests, and none had any complaints.

Tests excluded from group data. Both tests from the first patient to undergo the *e*SAM procedure were excluded from group data because the dosages used for the initial bolus and for the infusion were too low. Although it was clear during the patient's first test that the dosage was low, the same drug parameters were used for her second test so that the two could be compared without ambiguity. Because this patient began to recover function before the infusion was stopped, her two tests were similar to those performed with amobarbital. Thus the necessary clinical data were obtained, but her tests did not conform to our typical *e*SAM procedure. Similarly for the other two excluded tests (one each for two patients), the needed clinical information was obtained but the tests were not typical: in both cases, injection was opposite a very large lesion, resulting in somnolence throughout the period of infusion, which was therefore terminated. Thus the clinical data were obtained during the period of recovery, and the timing measures were not appropriate for inclusion in the group data.

Discussion. Etomidate appears to be a safe alternative to amobarbital for intracarotid speech and memory testing, with certain advantages. While our team was expanded to include an electroencephalographer and an anesthetist, we anticipate that as the test becomes routine, it will be performed with an EEG technician and the neuroradiologist, as was the case with the IAP. To date, the youngest patient we

Table 4 *Memory results (16 patients)*

Injection site	No. of injections	Performance			Awareness of contralateral power loss
		Passed	Failed	Borderline	
Ipsilateral to seizure focus, n (%)	12	11 (92)	0	1 (8)	8 (67)
Contralateral to seizure focus, n (%)	10	4 (40)	5 (50)	1 (10)	2 (20)
Two unoperated bilateral cases					
Case 1: R > L					
Ipsilateral	1	Pass R	—	—	Aware
Contralateral	1	—	Fail L	—	Aware
Case 2: L = R*					
L injection	1	Pass L	—	—	Aware
R injection	1	Pass R	—	—	Unaware

Ipsi- or contralateral to seizure focus determined by final clinical decision of abnormal side or by surgery.

* Neither side could be designated more abnormal for Case 2.

have tested with the *e*SAM procedure was 16 years old. However, etomidate has been used successfully with children in emergency departments (see Rothermel[22] for a review), including in children under the age of 10 years.[40] The expected effects usually associated with hemispheric anesthesia were observed: EEG slow waves ipsilateral to injection, loss of contralateral power, and speech arrest following dominant-hemisphere injections; further, facial asymmetry, visual field defect, and dysarthria were observed in several tests. An advantage of the *e*SAM procedure over the IAP is the ability to control the period of hemianesthesia. The first signs of recovery occurred only after discontinuation of the infusion, and as recovery was gradual, lasting about 4 minutes (see tables 2 and 3), testing could continue after the period of complete hemianesthesia. Therefore, in this sense *e*SAM provides a test similar to IAP. However, in addition *e*SAM provided an extended period of guaranteed hemianesthesia between bolus injection and the beginning of recovery (see figure 1).

On EEG, changes similar to those seen in amobarbital tests were observed using etomidate: slow-wave activity predominated in the injected hemisphere, but a lesser slowing occurred also in the contralateral frontal region in 75% of injections (compared to 78% with amobarbital).[6] The changes observed in the two patients with SEEG were also similar to those we find in patients tested with amobarbital.[30] Activation of interictal epileptic discharges after etomidate injection was seen in 8/24 injections (33%), always ipsilateral to the injection. Importantly, it was without behavioral changes.

The frequent unavailability of sodium amobarbital prompted a few centers to use methohexital, which is an ultra short-acting barbiturate and requires either extremely brief tests[10] or re-injection,[12] or both. If a test requires re-injection, the drug will have waned during testing before more is injected, resulting in a changing and unpredictable level of anesthesia during the cognitive tests. This is particularly problematic for interpreting memory test results, which will not be valid if the critical to-be-remembered items are not introduced during a sufficient drug effect.

Propofol has also been tried using the traditional procedure of a single bolus injection; two articles each reported a single case,[13,14] and a third reported a small series.[15] In the latter, a smaller dose was used compared to that used for the two previously reported patients. Those authors reported success at determining hemispheric dominance in all 12 of their patients, and at drawing conclusions about memory in 75% of them. The adverse effects described in the earlier reports—a sensation of intense blue light[13] and a hot sensation in the head[14]—were not observed. Although only minor adverse physical effects were reported in their sample (laughing, head and eye version in 25%), intra-arterial injection of propofol carries some risks related to its formulation in a lipid emulsion.[17] These are risks of pain upon injection, anaphylaxis, or hyperlipidemia.[34-37]

In our procedure, the physiologic reaction to etomidate injection was benign, in that there were no physical reactions other than the expected loss of power and, in some, visual field defect. The exception was a tremor, which occurred in 12 of 26 tests (46%) and was mild in most (83%) and may be related to the myoclonus that occurs in 20 to 45% of patients receiving etomidate for procedural sedation.[20,38,39] The type and quality of tremor in the absence of concomitant neocortical EEG epileptic abnormalities suggest an origin in subcortical structures.

PET or fMRI have been used to determine language dominance[41-43] and fMRI paradigms are being developed as an alternative to the memory evaluation component of the IAP.[44,45] However, it remains difficult to activate medial temporal lobe structures reliably with fMRI, and not all patients can tolerate MR imaging; thus it is unlikely that these methodologies will completely replace intracarotid anesthetic procedures in the near future. Further, tasks in the IAP or *e*SAM are both simple and flexible, allowing tests to be performed in patients at all intellectual levels and ages. It should be noted that different information is obtained from these two methodologies: activation imaging helps determine brain structures participating in the studied function, whereas the IAP/*e*SAM transiently disables most of one hemisphere, helping to predict the effects of surgery.

Our experience in 30 *e*SAM tests has shown that etomidate provides adequate hemianesthesia for performance of speech and memory testing, and continuous infusion is advantageous, allowing all behavioral testing to be completed during full drug effect. Etomidate may be a sound alternative to amobarbital for intracarotid anesthetic procedures.

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