Epilepsia, 43(9):1056–1061, 2002
Blackwell Publishing, Inc.

Sodium Methohexital (Brevital) as an Anesthetic in the Wada Test

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Summary: *Purposes:* We report our experience with sodium methohexital (Brevital) as an anesthetic used in the Wada test for language and memory in 86 epilepsy surgery patients (173 procedures).

Methods: The methods are compared with those of the more commonly used anesthetic sodium amobarbital (Amytal).

Results: Despite differences between the methohexital and amobarbital test protocols, the behavioral and neurologic effects of the two anesthetics are similar. Because of the brief duration of methohexital, two successive injections are made on each side rather than one, to lengthen the time available for testing both language and memory. Behavioral and EEG indices return to baseline more quickly and more completely with methohexital than with amobarbital, allowing several repetitions of the procedure without incremental drowsiness, and the total time taken for the procedure is less with methohexital than with amobarbital.

Conclusions: The results of language and memory testing in the Wada test are equivalent for amobarbital and methohexital, except that methohexital has a briefer duration of action and is associated with less sedation. **Key Words:** Brevital—Intracarotid—Wada test—Amobarbital—Methohexital—Injections—Intraarterial.

The Epilepsy Surgery Program of the University of Michigan Medical Center used sodium amobarbital (Amytal) in the intracarotid amobarbital procedure (IAP or Wada Test) in >200 patients between 1980 and 1998 as part of their evaluation for epilepsy surgery. Because of difficulty obtaining amobarbital in mid-1998, we began to use an alternative barbiturate, sodium methohexital (Brevital). We now report our experience with this anesthetic in 86 patients (173 procedures), with a detailed analysis of the behavioral and EEG recovery of 20 patients.

The neurologist Juhn Wada (1, translation in 2) reported the effects of unilateral intracarotid injection of amobarbital on language in an article published in Japanese in the late 1940s. While at the Montreal Neurological Institute in the 1950s, Wada introduced his technique into the presurgical evaluation of patients with refractory epilepsy to determine language lateralization before surgery (3). Within a few years, it became evident that the technique also could be used to exclude or modify surgery in patients with dysfunction to the memory mechanisms on the side contralateral to the proposed temporal lobectomy (4,5). For historical reviews, see Wada (6) and van Emde Boas (7). Very little has changed in the procedure since the 1950s. Femoral artery access is now used rather than a direct internal carotid artery catheterization, and the posterior cerebral artery (PCA) is occasionally used rather than the internal carotid for memory testing (8,9, but see 10 for a cautionary note). Whereas the test was initially given on 2 separate days for the two hemispheres, many centers now test both sides on the same day, despite findings that memory abilities of the second side may be disadvantaged when this is done (11).

Most centers around the world use amobarbital in the Wada test (see 12,13), and its brief action, low toxicity, and the vast experience with its effects contribute to its choice in carrying out this procedure. However, amobarbital is associated with troublesome characteristics. In particular, successive injections must be separated by ≥45 min (14), and after two injections, a third injection is likely to lead to significant drowsiness, which limits the number of times the test can be carried out on a particular day (see 11). This problem is less severe at centers where the right and left hemisphere injections

Accepted March 30, 2002.
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can be carried out on different days, but the number of such centers is small. During a brief hiatus in the availability of amobarbital in 1998, we began to use another anesthetic, methohexital. This substance is commonly used for the Wada test in France (e.g., 15) and several South American countries where amobarbital is difficult to obtain, and at a small number of institutions in the United States. Several articles have been published in which methohexital was used successfully for the test (15–18), and the distribution of the effect of the anesthetic appears to be the same for amobarbital and methohexital (15,19). However, there has been little discussion of the advantages and disadvantages of methohexital compared with amobarbital (see 20 for a report in French), and for this reason, we report here our recent experience with this anesthesia.

METHODS

Subjects

Eighty-six patients being evaluated for intractable epilepsy were tested. The average age was 35.1 ± 11.8 years. Range was 9.1–59.1 years. There were no significant differences in age between men and women or between left- and right-temporal lobe patients. Seventy-seven of the patients had a unilateral temporal epileptogenic region with mesial temporal sclerosis (MTS) as the most common pathologic substrate. In the other nine patients, the epileptogenic focus was parietal (one case), occipital (one case), frontal (one case), orbitofrontal (two cases), temporooccipital (two cases), frontoparietotemporal (one case) and orbitofrontal–anterior temporal–insula (one case). Patients received a full neuropsychological evaluation and a Wada test as part of the presurgical evaluation before epilepsy surgery. Handedness was determined by the Crovitz–Zener Handedness Questionnaire (a test assessing degree of hand preference on a scale of 1–5 for 14 activities, nine of which are performed with the dominant hand, and five of which are typically performed by the nondominant hand). Right handedness was defined as a score between 14 (completely right-handed) and 28. Mixed-handedness patients were those with scores >28, with evidence of preferring one hand for some tasks (e.g., writing) and the other hand for other tasks (e.g., throwing a ball), or both hands equally for more than half the tasks. Left-handedness was defined as a score between 28 and 70 (completely left-handed) with evidence of consistent preference for the left hand in at least half the tasks. Demographic details are provided in Table 1.

TABLE 1. *Demographic and injection characteristics for the 86 epilepsy patients*

Injections	Bilateral	71
	Unilateral	15
Sex	Male	43
	Female	43
Epileptogenic focus	Left	43
	Right	43
Pathology	MTS (38) or MTS/MCD (2)	40
	MCD (9) or MCD/MTS (3)	12
	Tumor: ganglioma (4), glioma (2), oligodendroglioma (2), oligoastrocytoma (1), ganglioma/MCD (1), hamartoma (1); unspecified (1)	12
	Cryptogenic	5
	Hippocampal dysplasia	4
	Cavernous angioma	3
	PXT (2) or PXT/MCD/MTS (1)	3
	DNET	2
	AVM	2
	Encephalomalacia	1
	Polymicrogyria	1
	Perinatal ischemic injury to temporal lobe	1
Age at time of procedure	9–12	4
	13–18	6
	19–50	67
	51–59	9
Handedness	Right	65
	Left	13
	Mixed	8
Language dominance	Left	80
	Right	3
	Bilateral	3

MTS, mesial temporal sclerosis; MCD, malformation of cortical development; PXT, pleomorphic xanthoastrocytoma; DNET, dysembryoplastic neuroepithelial tumor; AVM, arteriovenous malformation.

Procedure

Our protocol for the use of methohexital in the Wada test is similar to the method used at the University of Florida (16,18). Our current procedure is to test language abilities after an initial injection of 3 mg of methohexital over a 3s period and then present memory items after a second injection of 2 mg over a 2-s period. The second injection is given as soon as the patient begins to show signs of recovery from the first injection (usually resumption of contralateral grip strength from 0/5 to ≥2/5 or the beginnings of expressive language after injection into the speech hemisphere). We also have carried out memory testing after a superselective injection of methohexital into the PCA in nine patients (one of them on two different occasions), by using single or multiple injections of 1 or 2 mg over a 2- to 4-s period.

Of the 173 procedures reported here, 20 consisted of intracarotid methohexital injections of 4 mg followed by 3 mg (11 patients, two of whom also received a 3-mg injection followed by a 2-mg injection) and 137 procedures consisted of injections of 3 mg followed by one or more injections of 2 mg after a fixed (62 procedures; 32 patients) or variable (75 procedures; 40 patients) interval. Five procedures consisted of 2 mg followed by 1 or 2 mg (four patients, two of whom were young children), and one procedure consisted of a single dose of 3 mg (one patient). Nine of these patients (10 procedures) underwent follow-up testing of memory with 1- or 2-mg in-

jections into the PCA (Table 2). Of the 40 patients receiving 3 mg and then 2 mg, with a variable interval between the injections (our current method), 34 had bilateral procedures. Of the latter group, the records of a series of 20 patients were analyzed to determine average recovery times of the behavioral and EEG effects of the drug.

Angiography and preparation of anesthetic

Diagnostic angiography of the internal carotid artery distribution is performed in the usual manner (femoral approach; typical angiography followed by a second slower injection rate of 1 ml/s for 4–5 s to simulate the hand injection of the methohexital). If fetal origins of vessels to the brainstem are present, the test is either terminated or carried out with a higher positioning of the catheter or with a superselective injection of the PCA (useful only for memory testing).

The methohexital is reconstituted by using sterile water to a concentration of 10 mg/ml. This is subsequently diluted to a concentration of 1 mg/ml with sterile saline. In a typical procedure, we use a total of 5 mg of methohexital injected in doses of 3 mg followed by 2 mg. At the time of the first injection, a total of 3 ml plus dead-space volume of methohexital solution is injected at a rate of 1 ml/s. Fluid is then retracted from the catheter, the catheter is flushed, and ~20–120 s later, the second dose (2 mg) is injected by using the same flushing technique. On rare occasions, a third or fourth injection of 2 mg is made. The catheter is generally withdrawn to the aorta as soon as the memory test items have been shown to the patient after the last injection. Once the neurologic and neuropsychological testing is complete, this process is repeated on the contralateral side. Most patients are kept overnight on the neurology ward.

Behavioral testing

The behavioral protocol is based on the methods developed at the Montreal Neurological Institute (21). Unless there is reason to do otherwise, we carry out the procedure on both sides, starting with the epileptogenic hemisphere. Memory and language abilities are tested after the angiogram and just before injection of the anesthetic as a baseline. This baseline testing includes three memory items, which are tested for recall after distraction for ≥60 s, naming of common objects, reading of short words, spelling, serial functions (counting, reciting the days of the week forward and backward), and comprehension of verbal commands. A brief version of the same language testing is used again during the 60–90 s of drug effect after the first injection. As soon as language abilities have been determined, grip strength is tested and monitored until a level of 2/5 is regained or until expressive language begins to recover after injection of the speech hemisphere, whichever occurs first. With right-hemisphere injections or any injection in which the drug reaches the PCA via the posterior communicating artery, special care must be taken to counteract the patient's tendency to neglect the affected hand. Our clinical impression is that contralateral neglect with the right-hemisphere injection of methohexital is denser than that with amobarbital. For this reason, we generally suspend testing of the grip strength with the unaffected hand once it has been established that the patient can grip on command, and the affected hand is brought in front of the patient so it is in central vision. As soon as the beginning of recovery is noted, the neuroradiologist is asked to make the second injection (2 mg), and when grip strength has returned to 0/5, the memory items are shown; this takes ~30 s. Care must be taken to ensure that the injection is not made before the beginning of recovery to prevent obtundation. The memory items consist of five items (a real object, two line drawings of common objects, a large compound word on a card, and a sentence presented aurally and repeated by the subject if possible). The patient is asked to name the word and objects and to state their use; this information is provided by the examiner if the patient is unable to speak. An interference task follows to prevent rehearsal during the recovery. Grip strength and language abilities are monitored during the presentation of the memory items, and if evidence of recovery is seen before the last memory item is introduced, another injection (2 mg) is made; presentation of memory items resumes as soon as power decreases to 0/5 again.

Assessment of the patient's memory after recovery of motor functions and EEG begins with a test of memory for the preinjection materials. The quality of memory for the preinjection materials is used as a baseline against which memory for postinjection materials is judged. The patient is then asked to recall the postinjection items, starting with free recall and proceeding sequentially to hints, alternatives, and recognition. If the patient does not show convincing evidence of remembering the item, a forced-choice method is used, although credit for the memory is not given for correct guesses. Memory failure consists of recall of one or none of the five items; bor-

TABLE 2. *Injection parameters for 173 procedures in 86 patients*

Protocol (mg. injections)	Procedures	Number of patients	Cumulative unique patients
Fixed 3-3 or 3-3+	62	32	32
Variable 3-2 or 3-2+	75	40	+40 = 72
Variable 2-2 or 2-2+	5	4	+4 = 76
Fixed 4-3	20	11	+9 = 85 (2 patients also had 3-2)
One injection, 3 mg	1	1	+1 = 86
PCA	10	9	+0 = 86 patients total

PCA, posterior cerebral artery.

derline recall is two items; and a solid passing score is three or more correct items.

RESULTS

With methohexital, the expected neurologic and behavioral changes (hemiplegia, visual field cut, hemispatial contralateral neglect—especially with the right injection—and loss of speech with injection of the speech hemisphere) are indistinguishable from those seen after injection of amobarbital. Of the 86 patients, 71 had bilateral tests. Unilateral testing was carried out in 15 patients because of unusual vascular organization (one case), age younger than 12 years and low tolerance for the procedure (three cases), lateral cortical epileptogenic focus with a planned resection that would not include mesial tissue (three cases), emotional reaction after first injection and reluctance to continue the testing (one case), and restricted time in the angiography suite (seven cases, including two in which tests were carried out on the PCA after memory failure after injection on the side of the planned resection). At the time of writing, 79 (92%) of the patients have had a unilateral resection of their epileptogenic focus. None of these patients has had a significant postsurgical memory disturbance.

Language and memory outcome

The outcome of language testing of the 86 temporal lobe patients is shown in Table 1. Table 3 shows memory findings for a subset of 34 patients receiving bilateral injections of 3 mg and then 2 mg, with a variable delay between the injections (our current method). The incidence of right-hemisphere language, bilateral language, and memory scores for the nonepileptogenic hemisphere and the epileptogenic hemisphere are all similar to those obtained with amobarbital (21).

Motor recovery

With a 3-mg injection of methohexital, contralateral grip strength decreased from 5/5 to 0/5 within 2–3 s, and in the case of the hemisphere dominant for language, the person became mute. These behavioral changes lasted for ~90–100 s, at which point grip strength returned to ≥2/5 and/or the person began speaking again. After a second injection (2 mg), grip strength decreased to 0/5 again, and speech, if it was beginning to recover, ceased again. After a subsequent 110–120 s, contralateral grip strength will have returned to ≥3/5, which means that no further memory items can be introduced. If grip strength returns to 3/5 before all memory items are shown, a third injection of 2 mg is made. The total time from the first injection to behavioral baseline is ~260 s. On one occasion, we had to make a fourth injection because of particularly rapid recovery. Table 4 shows a comparison of motor recovery times for the most recent 20 patients who had bilateral injections. For comparison, the right column shows previously published data (adapted from 14) with a single 120-mg injection of amobarbital. With methohexital, time to motor recovery was the same for the left and right hemispheres [$t(19) = 1.0$; $p > 0.31$]. As expected (14), the motor recovery times were slightly longer for the nonepileptogenic hemisphere (second injection) than for the epileptogenic hemisphere (first injection), but the difference was of borderline significance [$t(19) = 2.1$; $p = 0.053$, two-tailed]. Motor recovery from the effects of methohexital (259 ± 63) is clearly much faster than that with amobarbital [31 patients with bilateral injections in whom motor recovery times were recorded: 385 ± 108; $t(49) = 4.7$; $p < 0.0001$].

EEG recovery

With the initial 3-mg injection of methohexital, the EEG changed from baseline to high-amplitude anteriorly predominant delta activity over the hemisphere ipsilateral to the injection, lasting 20–30 s. In about half the cases, there is an ~20% crossover slowing over the contralateral hemisphere, which rapidly dissipates within 10 s. After the subsequent 2-mg injection, the EEG again showed high-amplitude anteriorly predominant delta slowing that gradually evolved to lower amplitude delta–theta slowing, and returned to baseline ~360 s after the first injection. Usually overriding fast activity is observed over the hemisphere ipsilateral to the injection. In

TABLE 3. *Memory in 34 patients with bilateral injection of methohexital*

Functioning hemisphere	Pass	Borderline	Fail
Nonepileptogenic hemisphere	32	2	0
Epileptogenic hemisphere	13	9	12

TABLE 4. *Electrographic and motor recovery times*

	Methohexital (n = 20)	Amobarbital (n = 48)
Behavioral (motor) baseline		
Mean recovery to baseline (all injections)	259 ± 69	382 ± 114
Left hemisphere recovery	269 ± 72	389 ± 96
Right hemisphere recovery	250 ± 65	377 ± 133
Epileptogenic hemisphere recovery	247 ± 69	380 ± 126
Nonepileptogenic hemisphere recovery	272 ± 67	387 ± 113
EEG baseline		
Mean recovery to baseline (all injections)	355 ± 85	465 ± 121
Left hemisphere recovery	355 ± 80	475 ± 132
Right hemisphere recovery	354 ± 92	457 ± 113
Epileptogenic hemisphere recovery	344 ± 82	445 ± 126
Nonepileptogenic hemisphere recovery	365 ± 89	488 ± 113

(Mean number of seconds ± SD) with methohexital. For comparison, comparable data from previous patients in whom we used amobarbital are provided (adapted from 14).

no case was there activation of interictal epileptiform abnormalities with methohexital.

Table 4 shows a comparison of EEG recovery times for the most recent 20 patients who had bilateral injections, compared with similar data with 120-mg injections of amobarbital (from 14). As we already saw with amobarbital (14), EEG recovery after injection into the nonepileptogenic hemisphere (365 ± 89 s) took slightly longer than after injection into the epileptogenic hemisphere (344 ± 82 s), although the difference does not reach statistical significance [$t(19) = 1.2$; $p > 0.2$, two-tailed]. In all but one of the methohexital cases, the epileptogenic hemisphere was injected first, so the effect of injecting the epileptogenic hemisphere first or second could not be independently assessed independent of order, as was done with amobarbital (14). On average, the time to EEG baseline after methohexital (355 ± 76 s) is more rapid than that with amobarbital [42 patients with bilateral injections in whom EEG recovery times were recorded: 468 ± 110 s; $t(60) = 4.1$; $p < 0.0001$]. In addition, it is our clinical impression that the patient was more alert after recovery than with amobarbital. In cases in which the test was repeated, we found that the patient remained alert even after three or four separate tests, which would be unlikely with amobarbital.

DISCUSSION

Despite the similarities in terms of behavioral and neurologic changes, there were several notable differences between the methohexital and amobarbital Wada tests. First, the total time from the first injection to EEG baseline was almost 2 min faster for methohexital than for amobarbital (355 vs. 465 s). In addition, the patients recovered more completely after each injection, which allows multiple testings within a single session without the incremental drowsiness that is seen with amobarbital. Because it is not necessary to wait 45 min between injections, as had been the case with amobarbital (14), the entire procedure can be completed more efficiently with methohexital than with amobarbital; the time from the preinjection behavioral testing on the first side to completion of testing on the second side is usually <60 min. In our institution, the neuroradiologic team also prefers methohexital because it is an anesthetic that they already use in several other procedures, and the pharmacy here also has preferred not to handle amobarbital, which is a controlled substance used in small quantities by only one service. Finally, periodic irregularities in the availability of amobarbital have been troublesome, and an alternative barbiturate is desirable. In terms of the results of the procedure, the two anesthetics appear to be equivalent in their ability to determine which hemisphere is dominant for language function and to screen for the risk of amnesia after anterior temporal resection.

At high doses (25–50 mg), intravenous injections of methohexital can induce epileptiform discharges, and this effect has been is useful for pharmacologic activation during electrocorticography (22,23). However, with the low doses (5–9 mg) of intraarterial methohexital used for the Wada test, none of our patients showed activation of the interictal spikes.

Finally, it should be mentioned that because the EEG changes are faster and less obvious after methohexital than with amobarbital, the timing of the second injection and therefore the timing of the presentation of memory items must depend on an accurate and sensitive assessment of behavioral recovery (grip strength and language recovery) rather than electrocerebral changes, as is often the case when using amobarbital (13). This may lead to an apparent increase in the variability of the anesthesia parameters, but the vast majority of patients with intracarotid injections received 5–7 mg (158 of 163 intracarotid procedures or 97%). With Brevital, the clinical state of the patient determines the injection parameters. When a third (10 cases) or a fourth (one case) dose of 2 mg was injected during a procedure, this was because the patient began to recover before all the memory items could be presented.

Acknowledgment: We are grateful to Eileen Fennell of the University of Florida for her help in designing the protocol with methohexital. A preliminary version of these findings was presented to the Annual Meeting of the American Epilepsy Society, Orlando, Florida, December 3–8, 1999.

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