Motor and somatosensory evoked potentials in coma: analysis and relation to clinical status and outcome

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Abstract
Central sensory and motor conduction were studied in 23 comatose and three brain-dead patients. Motor evoked potentials (MEPs) to transcranial magnetic (magMEP) and electrical (eMEP) stimulation were recorded from the hypotensive muscle, and somatosensory evoked potentials (SEPs) were recorded after median nerve stimulation. Comparison of clinical with evoked potential (EP) findings revealed: 1) a painful stimulus applied to the skin of the arm lowered the excited threshold to cortical stimulation and was a prerequisite to obtain MEPS in 14 instances; 2) only in brain-dead patients were all EPs abolished simultaneously and bilaterally; 3) MEPS (p < 0.05, χ²-test), but not necessarily SEPs (p > 0.1) were preserved in the arms that showed normal motor reaction during clinical examination; 4) no correlation was found between EP findings and the Glasgow Coma Scale (GCS). The results of clinical and EP testing were examined in the light of the patient's outcome 10 months later: 1) fatal outcome was predicted by a GCS of three (38% of cases, p < 0.05, Fisher's exact test), abolished brainstem- or pupillary reflexes (38%, p < 0.05), the combination of these clinical signs (54%, p < 0.01), bilateral abolition of eMEPs (38%, p < 0.05), magMEPS (38%, p < 0.05), or SEPs (23%, p > 0.1), or a combination of clinical and EP data (85%, p < 0.0005); 2) good outcome was predicted by a GCS of ≥ 8 only in post-traumatic coma, and EPs did not help to predict quality of survival. It is concluded that EPs may be used to predict fatal outcome of coma; 1) if this appears impossible on the basis of clinical data alone; 2) if a second indicator is needed to confirm a clinical impression; 3) SEPs may be first evaluated during the acute stage of coma treatment, because they can be recorded in the presence of anaesthetic or relaxant agents; 4) MEP may be studied if outcome prediction remains ambiguous, and if the clinical situation allows for discontinuation of these agents.

Comatose patients can be examined clinically with a series of tests that help evaluate the severity of dysfunction of the cerebral hemispheres and the brainstem based on the application of appropriate stimuli and grading of the responses observed. The most widely used method is the Glasgow Coma Scale (GCS) that determines the patient's rating predominantly by their motor reaction to painful stimulation. Other factors of clinical significance, such as brainstem and pupillary reflexes, the patient's age and duration of coma, and the results of electrophysiological tests have been shown to improve the accuracy with which the outcome of coma can be predicted.

Somatic sensory evoked potentials (SEPs) are good predictors of the outcome of non-traumatic and traumatic coma. The recent development of transcranial electrical (eStim) or magnetic (magStim) stimulation of the motor cortex has allowed investigation of central motor pathways through the intact skull in clinical and research settings. Doubt has been cast on the value of motor evoked potentials (MEPs) to predict outcome of coma when using eStim, whereas the usefulness of MEP testing to magStim for this purpose has not been evaluated.

Thus the present clinical and electrophysiological study was designed to test in comatose patients how well the results of median nerve SEP and of MEPS reflect the actual severity of: 1) Coma; 2) Motor dysfunction; 3) Predicting the outcome of coma, and 4) Providing useful information that could not be obtained from the clinical data alone.

Material and methods

Patients
With the approval of the local ethical committee, 23 comatose and 3 brain-dead patients were studied; 16 of them were male (table 1). Their age was 16–75 (mean: 47) years. Patients with lesions of the spinal cord or peripheral nerves, fractures of the cervical spine, intracranial metallic bodies, epilepsy or intracranial aneurysms of the cerebral arteries were excluded. All patients had been in coma (that is, no speech, no eye opening, and no motor reaction to verbal commands) continuously for at least 24 hours before the study was begun. The aetiology of coma was traumatic in 11 and non-traumatic in 12 cases (table 1).

Patients were tested as soon as the clinical situation allowed discontinuation of sedative and muscle relaxant drugs for 12 hours, because unlike SEPs, MEPs in transcranial stimulation are particularly sensitive to a variety of centrally acting anaesthetic agents. The duration of coma (time...
interval between the onset of coma and the day of EP testing) was 1–50 days. The outcome of coma was assessed on the five-point Glasgow Outcome Scale (GOS) as fatal (I), vegetative (II), severely disabled (III), moderately disabled (IV), or good (V). The assessment was made after an average of 18 (range: 1–90) days in the patients who died, and after an average of 10 (6–20) months in survivors (GOS II–V) who had poor (GOS II–III) or good (GOS IV–V) outcome.

TEST PROCEDURE

Patients were first assigned a rating on the GOS, then pupillary and brainstem (corneal, oculocephalic) reflexes were assessed. Subsequently, median nerve SEPs (n = 26 patients, 52 sides), magnetic MEPS (n = 26, 52 sides) and electrical MEPS (n = 22, 44 sides) were tested. SEPs were assessed as reported previously, except that analysis-time was 100 ms, and 2 × 1024 stimuli were averaged on each side. Transcranial elStim was performed with anodal scalp shocks of up to 750 V applied over the motor area and using a high-voltage, low-impedance electrical stimulator (Type 180, Digitimer, Welwyn Garden City, UK). To avoid repositioning patients, some of whom were in a critical condition, the brachial plexus at Erb’s point was stimulated rather than the cervical roots over the spinous process of C7. Transcranial magStim was performed as described elsewhere using a commercially available device (Digitimer Ltd.), that had a stimulating coil of 8 cm mean diameter and that generated a magnetic field of 2 Tesla at maximal output of 2-5 kV.

Compound muscle action potentials (CMAPs) were recorded with surface electrodes taped to the belly and tendon of both abductor digiti minimi (ADM) muscles. The signals were fed into a recording unit (Medelec 94a, nbn-Electronic, CH-8142 Uitikon ZH) with the filters set at 30 Hz and 5000 Hz, and a gain between 70 μV and 5 mV/division, stored on a microcomputer, and printed offline on an x-y plotter (Hewlett Packard, CH-1217 Meyrin).

Intensities for cortical stimulation were set as high as necessary to obtain a CMAP from the contralateral ADM muscle. If no CMAP was obtained to two stimulations of maximal intensity in a patient at rest, the procedure was repeated twice together with a painful stimulus that was applied by twisting the skin of the inner surface of the upper arm. This manoeuvre, which was often followed by a motor arm reaction, was aimed to increase the excitability of motor pathways to cortical stimulation, because none of the comatose patients could contract their muscles voluntarily, and background contraction of the target and ipsilateral neighbouring muscles facilitates MEPs in awake subjects.

EVALUATION AND GRADING OF EVOKED POTENTIALS

Latencies of SEP components N9 (pexus), N13 (spinal), and N20 (cortex), and amplitudes N20/P25 were measured, and the mean of the two values was used for further evaluation. The upper limits of normal (+2 SD, n = 20 subjects, Vlach and Ludin: Thesis, Berne University, 1980) were N9: 11-3 ms; N13: 15-8 ms; N20: 22-3 ms; N13–N20 (central sensory conduction time, CSCT): 7-2 ms; side-to-side differences (Δ): latency ΔN13–N20: 0-95 ms; amplitude ΔN20/P25: ≤ 50%.

Onset latencies and baseline-to-peak amplitudes of CMAPs to elStim or magStim were measured. The upper limits of normal for magMEP with voluntary contraction of the
Table 2  Evoked potential grading criteria

<p>| | | |</p>
<table>
<thead>
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<tbody>
<tr>
<td>SEP</td>
<td>I</td>
<td>Normal CSCT (CCT ( &lt; 7.2 ) ms), side-to-side difference of CSCT ( \leq 0.95 ) ms</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Pathological CSCT or pathological side-to-side difference</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>N20 absent unilaterally</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>N20 absent bilaterally</td>
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| MEP | I   | Preserved muscle response bilaterally in the patient at rest |
|     | II  | Preserved muscle response only with simultaneous painful skin stimulation |
|     | III | Absent muscle response unilaterally |
|     | IV  | Absent muscle response bilaterally |

Somatosensory Evoked Potential (SEP) to median nerve stimulation;
Motor Evoked Potential (MEP) of the M abductor digiti minimi to transcranial stimulation; Central Sensory Conduction Time (CSCT)

ADM (mean \( +2.5 \) SD, \( n = 22 \) subjects, Walker, Hess and Schmid: Thesis, Berne University, 1991) were Cortex-ADM: 25-9 ms; Erb's point-ADM: 16-8 ms; cortex-Erb's point (modified central motor conduction time, CMCT): 9-8 ms; cortex-C7: 8-6 ms; Acortex-ADM: 1-9 ms; Acortex-Erb: 1-9 ms. Mean amplitudes were: cortex-ADM \( 4-9 \) (range: \( 1-2-8-7 \)) mV and Acortex-ADM: \( 1-1 \) (range: \( 0-4-2 \)) mV. No normal values were established for eIMEP, but their absence to eStim was considered abnormal. \(^{29} 30\)

SEPs were graded based on the presence or absence of the cortical response N20/P25, and of the CSCT\(^{17} \) (table 2). Grading MEPs was based on the presence or absence of CMAPs to transcranial stimulation\(^{3} \) (table 2). The absence of eIMEPs and magMEPs to cortical stimulation in the patient at rest was considered abnormal,\(^ {10-3} \) and an MEP was classified as absent if two consecutive cortical stimulations failed to elicit a reproducible CMAP of \( \geq 10 \) \( \mu \)V amplitude. Fisher's exact test was used to test association of: 1) Coma severity with EP data, or 2) Outcome with coma severity and EP data. The \( \chi^2 \)-test was used to test the association between motor responses to clinical and EP testing in the same arm.

Results

Table 1 summarizes the severity of coma

Table 3  Prediction of fatal outcome in the 13 comatose patients who died later

<table>
<thead>
<tr>
<th>Data</th>
<th>Number of patients</th>
<th>%</th>
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<tbody>
<tr>
<td>GCS 3</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Reflex pathology (oculoc cephalic, corneal, pupillary reflexes)</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>Age ( \geq 60 )</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>GCS 3, or reflex pathology</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>GCS 3, or reflex pathology, or age ( \geq 60 ) y</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>SEP IV*</td>
<td>3</td>
<td>23</td>
</tr>
<tr>
<td>eIMEPs IV</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>magMEPs IV</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>eIMEP or magMEP IV</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>eIMEP or magMEP or SEP IV*</td>
<td>9</td>
<td>69</td>
</tr>
<tr>
<td>GCS 3, or SEP IV</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>GCS 3, or eIMEPs IV</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>GCS 3, or magMEPs IV</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>GCS 3, or eIMEP or magMEP IV</td>
<td>9</td>
<td>69</td>
</tr>
<tr>
<td>GCS 3, or eIMEP or magMEP or SEP IV*</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>GCS 3, or reflex path or SEP IV*</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>GCS 3, or reflex path or eIMEPs IV</td>
<td>9</td>
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<td>62</td>
</tr>
<tr>
<td>GCS 3, or reflex path or eIMEP or magMEP IV</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>GCS 3, or reflex path or eIMEP or magMEP or SEP IV*</td>
<td>11</td>
<td>85</td>
</tr>
</tbody>
</table>

\( \% \) (of the 13 patients who died later on): Glasgow Coma Score (GCS); Sensory Evoked Potentials (SEPs) to median nerve stimulation; Motor Evoked Potential (MEP) to transcranial electrical or magnetic stimulation; (Grade IV) evoked potential: Response abolished on both sides

\( ^* \)one of the patients with grade IV SEP survived in a vegetative state.

(ADM), brainstem and pupillary reflexes, results of EP testing in the 26 patients, and outcome. Thirteen of the 23 comatose patients died, and of the 10 patients who survived, the outcome of coma was poor in four, and favourable in six patients. ElMEPs and magMEPs to cortical stimulation were obtained in 20 and 24 arms of patients at rest, whereas simultaneous painful skin stimulation was necessary to obtain MEPs in another five and nine arms. CMCT was \( 4-6-14-4 \) ms for eIMEP, and \( 5-0-14-4 \) ms for magMEP, CMCT of magMEP being \( > 9-8 \) ms in 10 instances. Cortical SEPs were preserved in 36 arms; CSCT was \( 5-19-3 \) ms (\( > 7-2 \) ms in nine instances).

CLINICAL MOTOR ARM REACTION AND EVOKED POTENTIALS

Comparison of the motor pattern assessed clinically,\(^ {2} \) and the corresponding results of EP testing for each arm separately (\( n = 52 \) arms) revealed that MEPs were less frequently preserved when the arm was paralysed, pathologically extending or flexing, than when motor activity in the arm was appropriate withdrawal or localisation; this correlation was statistically significant for eIMEP (\( p \leq 0-05 \)), but not for magMEP (\( p > 0-1 \)). In several instances MEPs could be elicited (either without or only with painful skin stimulation) from an arm that was completely paralysed, although no motor reaction was visible clinically with the same painful skin stimulation. The presence or absence of SEPs and motor activity in the same arm did not correlate significantly (\( p > 0-1 \)).

Only in the three brain-dead patients (table 1) were EP to all three stimulation modalities abolished simultaneously. The sensory plexus component N9 and CMAPs to plexus stimulation were preserved in three, the spinal SEP component N13 was present in two of the three patients. In the 23 comatose patients, no statistically significant correlation was found between results of EP and severity of coma.

Only patients who died later (table 1 and 3) had a GCS of three, absent pupillary- or brainstem reflexes on at least one side (\( p \leq 0-05 \)) or bilaterally abolished (grade IV) eIMEP (\( p \leq 0-05 \)) or magMEP (\( p \leq 0-05 \)); grade IV SEPs were seen in patients with either GOS I (\( n = 3 \)) or II (\( n = 1 \)). Each of the patients who were \( \geq 60 \) years of age died (\( p \leq 0-003 \)). A combination (table 3) of various parameters predicted fatal outcome of coma in up to 11 of 13 patients (85%, \( p \leq 0-005 \)). On the day of EP testing, duration of coma in those patients that had fatal, poor or good outcome was nine (range: \( 2-33 \)), 28 (6–50) and 11 (3–20) days, respectively; prediction of fatal outcome therefore was usually not possible on the basis of a long coma duration alone.

Survivors (table 1) always had GCS \( \geq 4 \), bilaterally preserved brainstem and pupillary reflexes, and at least unilaterally preserved EP (grade I–III) (\( p \leq 0-05 \)). Patients with GCS of 8–11 had a good outcome from post-traumatic coma, whereas a GCS of 4–7 was observed in cases with poor or favourable outcome. Predic-
tation of quality of survival was not improved by combining clinical and EP data, and was exceptionally improved by additionally considering the duration of coma.

**Discussion**

Two patients in this study suffered from severe structural brain damage (table 1), and the influence of anaesthetic agents on the clinical condition, the presence of a metabolic disorder, or a surgically treatable space-occupying lesion had been ruled out. None of the patients obeyed verbal commands; three of them fulfilled the criteria of brain death, and the other 23 were in coma with GCS between three and 11. Thirteen of the 23 comatose patients died within 1–90 days after testing, and 10 remained alive during a follow up period of six to 20 months.

To avoid drug interference with MEP recording, the study was not done until after the clinical condition of the patient allowed for reduction of centrally acting anaesthetic substances to minimal levels for 8–12 hours. This prerequisite prevented us from testing many likely candidates; in other cases, testing was only feasible after the first weeks of coma had elapsed (table 1)—the period when information additional to the results of clinical testing would have been most useful to help in predicting the outcome of coma. Thus in some of these patients, the long duration of coma until the day of EP testing would already have been highly predictive for the outcome of coma.

Technically, SEP and magMEP testing was easy to perform, whereas e1MEP testing could not be completed in four of the comatose patients due to a strong motor reaction to the painful electrical shock. The procedure was, however, time consuming, and it usually required two experienced technicians 1½–3 hours to complete each test. Usually, 6–8 cortical stimuli were needed to complete the elMEP and magSEP studies, respectively. No epileptic phenomena were observed clinically, and cortical stimulation had no measurable effect on vital parameters such as blood pressure and heart beat rate.

**CLINICAL FINDINGS AND EVOLED POTENTIALS**

Only in brain-death was central motor and sensory conduction abolished bilaterally and simultaneously. The plexus SEP component N9 and CMAPs to plexus stimulation were preserved, and the spinal SEP component N13 was present in two of the three patients. Similar results have been observed by others who studied SEPs to median nerve stimulation in brain death, whereas no such studies have been reported so far with MEPs to elStim or magStim. However, such findings must be viewed with extreme caution because the SEP changes in one, and the MEP changes in all three of our cases could also have been due to an isolated infratentorial or cerebral lesion, which could not be ruled out with the EP techniques used in this study.

The commonest finding in coma of all severities was the loss of MEPs to transcranial stimulation, or of cortical SEPs to median nerve stimulation, whereas CMCT (magMEP) and CSCT exceeded the upper limits of normal controls only in a minority of cases (table 3). Transcranial stimulation performed in the patients at rest was insufficient to elicit MEPs with either one or both stimulation modalities in 15 cases, a finding that must be considered abnormal. In some of the patients, clearly discernible MEPs appeared only when the cortical stimulus was administered together with a painful twisting stimulus to the skin of the upper arm.

The finding that EPs obtained in each stimulation modality could be affected independently in coma (table 1) indicate that the disease had affected various central pathways to a different degree, since SEPs are conducted through the lemniscal system and the thalamocortical afferents to the postcentral gyrus, and MEPs descend through the pyramidal tract, that is activated either at the axonal hillock of the pyramidal cells (elStim) or transynaptically through cortical interneurons (magStim).

The finding that painful stimulation of the skin was necessary to elicit MEPs to both stimulation modalities in some of the patients, obviously indicates that this skin stimulation acted as afferent facilitatory input to the motor pathways. The site and mechanisms of such facilitation, cannot be determined on the basis of the present data. The phenomenon seems complicated and may involve a rise in the excitability of the spinal motor neuron pool and probably also supraspinal or cortical elements via sensory afferents. In our group of 23 comatose patients, the spinal SEP component N13 was always present, and in most of the cases where facilitation by a painful skin stimulation was effective the cortical SEPs were preserved, thus indicating that sensory afferents conducting part of this facilitatory input were viable.

**PROGNOSTIC VALUE OF TESTS**

Each of the clinical and EP tests used in this study assesses a different spectrum of pathways. Therefore, a combination of clinical evaluation and various EP tests promises to provide a better indication of the functional status of patients, and therefore a better prediction of the outcome of coma than any of these modalities alone. The results of this study confirm the findings of others that the clinical signs, rather than the results of multimodality EPs, are the single most powerful factor in predicting outcome of coma, and that outcome prediction is improved when the patient’s age, the duration of coma, and the results of recording SEPs to median nerve stimulation are also taken into consideration. In contrast to the findings of others who studied elMEPs, this was true when the results of recording elMEPs and magMEPs were used as an additional tool in this study.

Fatal outcome of coma was predicted by the features listed in table 3. Except for one patient who survived in a vegetative state even with
bilaterally abolished SEPs, none of these criteria gave a falsely pessimistic prediction of death. Various combinations of the above clinical and EP criteria improved prediction of fatal outcome to up to 85% of cases. Prediction of the quality of survival in patients who survived based on their clinical status and EP test results, was more difficult, as has been noticed by others.4 A GCS of 8–11 in combination with preserved brainstem and pupillary reflexes predicted good outcome in post-traumatic, but not in non-traumatic coma, whereas a GCS of 4–7 and EP results in general were of no value in predicting the quality of survival of coma of either aetiology. From the results of this study, and from the current literature we have drawn three conclusions:

1) Performing EP studies may be desirable in those cases where predicting the outcome of coma appears impossible on the basis of the clinical data alone; or if a second indicator is needed to confirm a clinical impression. In this situation EP testing is useful solely to reinforce the prediction of fatal outcome, but not to predict the quality of survival. The clinical circumstances may then decide which of the EP tests should be applied first, and whether one or two of them can be omitted or postponed.

2) SEPs may be first evaluated during the acute stage of coma treatment, because SEPs, 17, 19 but not MEPs20–23 can be recorded when the patient is relaxed and under the influence of anaesthetic agents. EP testing in an early stage of coma seems to be especially desirable because outcome prediction is most difficult in this stage4 and SEPs have proved useful in early prognosis in coma. 3 4 If SEPs are abolished bilaterally, the results of this study and of others10 indicate that this is highly predictive of a fatal outcome of coma, and further studies may be omitted.

3) MEP studies may be performed only if necessary, and as soon as the clinical situation allows for discontinuation of short-term analgosedation, or short-term mechanical ventilation, of sedative and relaxant drugs. Magnetic stimulation may be the first choice for early testing after skull surgery in the presence of a fresh wound, or of a large postoperative skull defect; or if the patient is likely to show excessive motor or vegetative reaction to pain. Electrical stimulation may be used in patients in whom no pain reaction is expected, or where safety reasons (see exclusion criteria) rule out the use of transcranial magStim.

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