Evoked potentials in severe head injury—analysis and relation to outcome

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SUMMARY Somatosensory, visual and auditory cortical and brainstem evoked responses were obtained from 32 patients with severe head injury. A simple count of the number of waves present in the various responses provided the optimum method of analysing the data. The results of each cortical response, but not of the brainstem response, correlated with outcome, and a combined assessment gave the highest correlation. The data provided only slight improvement on predictions based upon clinical features.

Clinical features which reflect the severity of brain dysfunction are extremely important in monitoring the progress of the head injured patient and can give reliable prediction of outcome, but a more detailed assessment of anatomical and functional disorders in the brain may be provided by a variety of investigative techniques. These include CT scanning, measurements of intracranial pressure and cerebral blood flow, and analysis of the EEG and sensory evoked potentials. Interest in evoked potentials has been stimulated by the availability of computer averaging as a routine technique and responses in auditory, visual and somatosensory systems have been studied both individually and in a multimodal approach.

The value of investigative techniques, either in monitoring a patient’s progress or in predicting outcome, depends upon their ability to provide information additional to that available clinically, or in their being suitable to use in patients who have been rendered inaccessible to assessment as a consequence of sedation and muscle relaxation. We have studied auditory cortical (AEP), auditory far field (BAEP), somatosensory (SEP) and visual (VEP) evoked responses in severely head injured patients in order to determine what practical problems were encountered in their recording, what methods of analysis were appropriate, and the extent of inter-dependence between the results of different responses. We also aimed to discover how well the results correlated with outcome and, finally, whether the data provided predictive information additional to that available from clinical assessment.

Methods of recording and patients studied

Stimulating and recording apparatus

Silver/silver chloride electrodes were applied to the head with collodion, according to the 10-20 placement system. Electrode impedance was maintained at about 2 Kohms. The recorded signal was amplified (× 10³) (Devices Amplifier No. 3542, input impedance 10 megaohms) averaged (Datalab Unimac No. DL4000; 1024 bits; digitising rate 100 KHz) and plotted with an XY recorder (Hewlett Packard No. 7035B) (fig 1). A 10 microvolt square pulse was fed through the system for calibration prior to each recording session.

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Fig 1 Block diagram of stimulating and recording apparatus used to elicit evoked responses.
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BAEP

The auditory far field response was recorded from each ear in turn (vertex active; ipsilateral mastoid reference). Clicks of 70 dB intensity and 300 μs duration were delivered to the ear under study at 12 Hz while the opposite ear was masked; 2048 responses were averaged. In the intensive care unit the optimal band pass was 490-1000 Hz. The sweep length was 20 ms, but waves occurring beyond 11 ms were not included in the analysis.

AEP

Auditory near field responses were recorded from vertex (active) and mastoid (reference) electrodes. An 80 dB, 300 ms white noise stimulus was applied to both ears at 0.5 Hz; 128 sweeps were averaged. The optimal band pass was 0.45 to 50 Hz with a sweep length of 600 ms.

SEP

Somatosensory evoked responses obtained by median nerve stimulation at 5 Hz were recorded simultaneously from each hemisphere (C3, C4 active; vertex reference). The voltage of a 0.2 ms pulse was increased until thumb twitching occurred. In the two paralysed patients, a 60 volt stimulus was used. The sweep length was 200 ms, 512 sweeps being averaged; band pass was 0.45 to 1000 Hz.

VEP

Visual evoked responses were recorded from each occipital electrode (01, 02) with vertex as reference. A “C” flash stimulus was used (duration 100 μs) at 2.5 Hz (Devices Photo Stimator, type 3182). The optimal band pass was 0.45 to 100 Hz; 128 sweeps were averaged with a sweep length of 300 ms. Each eye was stimulated in turn. On each occasion evoked responses were recorded simultaneously from each hemisphere.

After recording the response to each sensory modality, the base-line electrical activity (EEG) was averaged at the corresponding stimulus frequency. Mains interference in the intensive care unit was minimised by using shielded leads, by surrounding the patient’s head with a metal shield and by repeatedly checking electrode impedance.

Subjects studied

Normal subjects. Volunteers (nine males and two females) with no visual or auditory deficits or relevant past medical history formed a control group. Ages ranged from 17 to 67 years.

Head injured patients. Thirty-two patients (24 males and eight females) who were in coma for at least 6 hours following head injury were studied by evoked response analysis. Coma was defined as an inability to obey commands, to speak or to open the eyes.10 Eye opening, verbal response and motor response were each graded at the time of the evoked response study and the performance on the respective scales summed into an overall score.11 Patient scores could range from 3 to 15, the former being the least responsive. Their ages ranged from 4 to 74 years (median 24 years). The day of the study ranged from 1-13 days after the injury (median day 3). At the time of the study 29 patients were in persisting coma. Hearing and visual status were not known. Eight patients were receiving anticonvulsants (phenobarbitalone and epanutin, either singly or in combination); eight patients were treated with penicillin and sulphadimidine; and one patient was receiving heparin and frusenime. Two patients were paralysed (Pavulon) and ventilated. Outcome was assessed 6 months after injury on the five point scale described by Jennett and Bond.12 In addition, on each patient a predicted outcome was made on the basis of their clinical state at the time of the evoked potential study.1 Due to the non-normality of the data (fig 6) and to the fact that some of the data, such as the outcome scale, could only be graded rather than quantified, Rank Spearman correlation coefficients were used for all data analysis.

Results

METHODS OF ANALYSIS

In normal subjects we measured wave latencies and peak to peak amplitudes. Mean values and ranges were obtained for positive and negative waves in each sensory modality. The evoked potentials were directly comparable in any one specific modality between one normal individual and the next. By contrast, the wave forms evoked in head injured patients were seldom comparable. Waves were often absent or, if present, were delayed and of small amplitude. In addition, difficulties in recording caused by patient movement, electrical interference, or inherent wave rhythms, resulted in sufficient irregularity of the averaged EEG baseline to cast doubt on the validity of small “evoked” waves. Therefore, in order to minimise the possibility of including artefacts among the wave forms analysed, we considered “significant” only those waves larger than the peak to peak EEG waves (fig 3). To ensure consistency this approach was also employed in analysing recordings from normal subjects.

We attempted to match the evoked responses we observed to the four tier grading system, based on wave latencies described by Greenberg et al.7 This proved to be possible in only a minority of cases since wave latencies seldom tallied with those described in each grade. Analysis of the results was therefore conducted at two levels of complexity; first, we noted for each modality whether wave forms were present or absent; second, we counted the number of positive/negative waves in each specific modality (following convention, only positive waves were scored in the BAEP). Only the SEP contralateral to the side of the stimulus was analysed because the ipsilateral response is considered to arise mainly from volume conduction.10 The optimal VEP irrespective of the side stimulated, was analysed for each hemisphere.
EVOKE D POTENTIALS

a Normal subjects
Representative wave forms for each modality from normal subjects are shown in fig 2. Positive waves are downgoing. Table 1 shows wave latencies and peak to peak amplitude for each sensory modality obtained from 11 normal subjects. Values for wave latency and amplitude often vary from study to study, for example SEP. This may be due to variation in recording bandwidth, auditory and visual stimuli intensity or electrode location. Our results are comparable with previous studies.

![Image of wave forms for normal subjects]

**Fig 2** Somatosensory (parietal, vertex), visual (occipital, vertex), auditory cortical and brainstem (vertex, mastoid) responses in normal subjects.

b Patients
In severely head injured patients the pattern of evoked responses seldom resembled those of normal subjects. Figs 3, 4, 5 show a range of evoked wave forms obtained for BAEP, AEP, VEP and SEP in patients in coma after head injury. The waves included in the analysis have been marked. The number of wave forms occurring in each modality for both patients and normal subjects is shown in fig 6. The upper and lower extent of the vertical line indicates the range; the heavy line indicates the median value, and the surrounding box contains

![Image of wave forms for patients]

**Fig 3** Auditory cortical (upper) and brainstem (lower) evoked response patterns in four different patients (vertex, mastoid). "Significant" waves are marked.

![Image of wave forms for patients]

**Fig 4** Somatosensory evoked response patterns from four different patients (parietal, vertex). "Significant" waves are marked.

**Table 1** Wave latencies and amplitudes in 11 normal subjects

<table>
<thead>
<tr>
<th>Latencies (ms ± SD)</th>
<th>Amplitudes (μV ± SD)</th>
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<tbody>
<tr>
<td>SEP</td>
<td>VEP</td>
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<tr>
<td>P1 24 ± 3; N1 33 ± 3; P2 46 ± 5; N2 61 ± 11; P3 80 ± 11; N3 114 ± 39; P4 131 ± 19; N4 140 ± 21</td>
<td>N1 72 ± 13; P1 119 ± 12; N2 162 ± 14; P2 213 ± 25; N3 242 ± 25; P3 277 ± 5</td>
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<tr>
<td></td>
<td>VEP</td>
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<tr>
<td>N1 36 ± 1-7; P1 9-0 ± 5-4; N1 10-1 ± 5-9; P2 7-6 ± 4-7; N3 6-5 ± 3-3; P3 7-7 ± 1-4</td>
<td>N1 5-1 ± 2-5; N2 6-5 ± 3-5; N3 5-6 ± 3-6; P4 6-2 ± 2-6</td>
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</table>
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![Graph](http://jnnp.bmj.com/)

**Fig 5** Visual evoked response patterns from four different patients (occipital, vertex). "Significant" waves are marked.

![Graph](http://jnnp.bmj.com/)

**Fig 6** Number of waves occurring in each modality for patients and normal subjects. The upper and lower extent of the vertical line indicates the range. The heavy horizontal line indicates the median value. The box contains half the total number of observations.

half the total number of observations. The wave counts from those responses which contained cortical components differed considerably in the head injured patients as compared with the normal subjects. On the other hand, the values for the BAEP were similar in the two groups.

**CORRELATION WITH CLINICAL STATE**

Twenty of the 32 patients had a coma score of five or less at the time of the examination; only three had coma scores greater than eight. There was a significant correlation between patient's overall coma score and the complexity of either their best or worst somatosensory evoked response (p < 0.001), and with their visual evoked responses (p < 0.005) but not with their AEP or BAEP. In addition, by itself, the motor response component of the scale provided similar correlations (SEP, p < 0.001; VEP, p < 0.005; wave sum, p < 0.001).

**CORRELATION WITH OUTCOME**

The distribution of outcomes 6 months after injury are shown in table 2, compared with the distribution of patients included in the international data bank. The use of the simplest approach to analysis, to note the presence or absence of waves in each modality and then count the number of modes with significant waves, provided a significant correlation with outcome (r = 0.682; p < 0.001). On the other hand, table 3 shows that in the majority of patients waves were obtained in all four modalities and that when this was the case the possible outcomes covered all categories, including vegetative state. This simple form of analysis therefore provided only limited discrimination.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>The distribution of outcome 6 months after injury in evoked study group and the International Data Bank</th>
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<tbody>
<tr>
<td>Evoked study</td>
<td>International Data Bank</td>
</tr>
<tr>
<td>Good recovery (GR)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Moderate disability (MD)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Severe disability (SD)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Vegetative state (V)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Dead (D)</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Number of modalities showing evoked waveforms related to outcome categories in 29 patients</th>
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<tbody>
<tr>
<td>No. of modes</td>
<td>Outcome</td>
</tr>
<tr>
<td></td>
<td>D</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
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<td>3</td>
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r = 0.682, p < 0.001 (abbreviations as in table 2).

Comparison of the number of identifiable waves in a particular modality with outcome gave results that differed from modality to modality. For the SEP and VEP both the best (B) and worst (W) hemisphere response were analysed. Table 4 illustrates the result obtained for SEPW. Rank correlation of the number of waves in each response against outcome extracted the maximum information from the data available and we derived quotations for the correlation of each modality with outcome (table 5). With the exception of the BAEP, all modalities correlated significantly with outcome. The SEPW showed the highest correlation of individual responses (r = 0.676; p < 0.001). However, summation
The extent of inter-dependence of the results from different modalities is illustrated in Table 7. Somato-sensory evoked responses (B and W) correlated strongly with both AEP and with VEP from both hemispheres. VEP and AEP were not inter-correlated and BAEP wave numbers showed no correlation with the results of any other mode of stimulation.

Predictions of outcome based on the patient's age and on clinical state were made for each of the 32 patients, using the prognostic criteria derived from the international data bank. We used a cost function to assess whether the additional information provided by evoked response data could improve on these predictions. The number of patients were too few to be conclusive but only a marginal improvement was suggested.

Discussion

Evoked potentials are now widely used in neurological investigation but most studies reported involve conscious and co-operative patients. This study has confirmed that analysis of sensory evoked potentials can provide information about the severity and distribution of brain damage in patients in coma after head injury. In addition, it has identified more clearly than previous studies, the problems that are encountered in performing evoked potential studies in these patients, and attempted to define the value of these studies as compared with clinical methods. We will consider how far it is possible to answer certain outstanding questions; what electrical events should be analysed; how should analysis be performed; what is the information yielded by evoked potential analysis; what are the likely values...
of evoked potential studies, both at present and in the future?

**Data Acquisition and Analysis**

There are problems in recording evoked potentials from a patient in coma following severe head injury, that make analysis of results difficult. These problems may be due to patient movement or to background interference which we have found to be common in intensive care units. Moreover, wave forms may be either delayed or absent as a consequence of brain damage. It is therefore essential to assess the authenticity of any evoked pattern either by comparison with a consecutive average of background activity or by multiple consecutive averages.\(^{17}\)

In the former only waves with peak to peak amplitude larger than those occurring in the averaged background activity should be considered significant. This method minimises the inclusion of artefacts in the analysis, even although this may be at the expense of excluding small amplitude evoked potentials. When waves are absent, the appropriate end-organ may be tested by recording the cochlear microphonic, the electroretinogram or the cervical response. In practice we found this unnecessary, since bilateral end-organ damage was seldom encountered and evoked responses were not considered in isolation.

Wave amplitudes and latency can both be used to compare the evoked responses in patients with those of normal subjects but, because amplitude is very variable in normals, ordinarily only latencies are compared. The problem with head injured patients is that the evoked response patterns become so distorted that identification of an individual wave is often impossible. Furthermore, additional difficulties occur with auditory responses because the integrity of the peripheral sensory organ is usually unknown at the time of examination and the presence of coma by itself can produce impairment of hearing.\(^{18}\) As BAEP latencies are intensity related,\(^{5}\) increased latencies may be found in the absence of brainstem damage.

Greenberg et al.\(^{7}\) attempted to cope with these problems by applying a four level grading system to each modality of response, the grades relating to increasing deviations from the normal. These workers, in order to make correlations of their results with the patient's clinical state and with outcome, compressed the grades into two groups. We attempted to fit the evoked wave patterns we observed in our head injured patients into Greenberg's system but this proved impossible in most patients owing to differences in wave latencies. Therefore, the data was analysed at two levels of complexity; firstly by merely noting the absence or presence of any identifiable waves in each modality and secondly by counting the number of wave forms present in each response within the specified time period. Indirectly, this method can reflect marked decrease in amplitude or increase in latency because small waves become lost in the background noise and late waves become delayed beyond the time of recording. Both the number of waves in individual responses and the summation of waves from all responses provided a useful index of dysfunction that could be correlated with clinical features and outcome.

**Correlation of Evoked Responses with Clinical State and Outcome**

Greenberg et al.\(^{8}\) found that decorticate and decerebrate posturing correlated significantly with all evoked responses except the BAEP, and concluded that the brainstem may not be as important as cerebral hemisphere function in determining posture. In our study the optimum motor response (that is localisation, flexion, extension or no response) rather than the presence of abnormal posturing correlated with SEP and VEP but not with BAEP and AEP. With the exception of this last finding our results are in agreement with Greenberg's conclusions.

Significant correlations between the SEPs and outcome were noted by Greenberg et al.\(^{8}\) and by Torre et al.\(^{5}\) It is not clear from the reports of either of these studies whether the "best" or "worst" hemisphere was studied. We found that responses from either hemisphere correlated significantly with outcome but it was the number of waves in response from the poorest hemisphere which gave the highest correlation. In our previous studies employing clinical criteria for prognosis we have emphasised the value of taking account of the response from the best side but this was because we placed the emphasis on avoiding pessimistic predictions. In the present analysis this bias was not introduced and the results are in agreement with a similar analysis based on clinical criteria.\(^{19}\)

In contrast to previous studies we found that, in addition to SEP, both VEP and AEP also correlated strongly with outcome. Failure to detect these additional correlations in previous studies may be due to differences in methods of data collection or analysis. Lack of correlation between BAEP and outcome is not surprising as these potentials appear to be extremely resistant to brain damage and may even be present in deep barbiturate coma (Siddell—unpublished observations). A recent study, however, looking specifically at alteration in brainstem amplitude and latency suggests that even this response may be related to outcome.\(^{20}\)

Multimodal evoked potentials indicate functional
activity in different sensory systems so that summation of the responses from each modality might be expected to provide a useful global index of cortical and brainstem dysfunction. This was confirmed by our finding that the highest correlation with outcome was given by such an index. On the other hand, even the most simple analysis which incorporated all modalities (that is counting the number of modes with waves present) also produced significant correlation with outcome.

Collection of multimodal data is time, personnel and effort consuming and it must be asked whether the return rewards input. Because the various cortical modalities are to some extent interdependent, it may be sufficient, in practice, to restrict the studies to somatosensory responses, reserving additional studies for special circumstances.

Even the recording of somatosensory evoked responses involves an effort and expenditure of time and personnel above the present capabilities of most neurosurgical intensive care units. It is not yet clear that the technique offers advantages in routine practice over clinical methods of patient assessment. The recording of multimodality evoked responses merely in order to assess prognosis would only be useful if it provided information that substantially improved predictions based on information which can be elicited at the bedside by any clinician. In paralysed patients, on the other hand, any method which permits monitoring of central nervous system function is of clear value and this may provide their most obvious immediate application.

This investigation was performed as part of a study of prognosis of severe head injury, and supported by an MRC Programme Grant to Mr G Teasdale and Professor B Jennett. Mr KW Lindsay was in part supported by the Wellcome Trust. We thank our colleagues in the Institute of Neurological Sciences for allowing us to study patients under their care.

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