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Short latency somatosensory evoked potentials and brain-stem auditory evoked potentials in coma due to CNS depressant drug poisoning. Preliminary observations

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Summary In patients in coma due to severe CNS depressant drug overdose the central somatosensory conduction time (CCT) after median nerve stimulation is prolonged and N20 is dispersed. Brain-stem auditory evoked potentials demonstrate delayed interpeak latencies (IPLs) I–III, III–V and I–V. This was observed in 4 out of 5 patients investigated after intake of an overdose of amitriptyline (2 cases), barbiturates, meprobamate and nitrazepam (one case each). Toxic levels of drug overdose were related to prolonged CCT and IPLs, whereas normal CCT and IPLs were found at the therapeutic drug plamsa levels. CCT, IPLs and dispersion of N20 decreased during the course of coma. All patients were successfully treated. It appeared that SSEP and BAEP investigations could make a distinction between a 'toxic' and a 'therapeutic' coma level in severe drug overdose. It further appeared that normalization of CCT and IPLs preceded clinical improvement.

Key words: Short latency SEPs; BAEPs; Sedative drug overdose; Toxic coma level.

The short latency somatosensory evoked potentials (SSEPs) and the brain-stem auditory evoked potentials (BAEPs) are remarkably unaffected by sedative drugs given in doses sufficient to render the EEG isoelectric (Stockard and Sharbrough 1980; Chiappa 1983b; Stockard and Iragui 1984) or to abolish all clinical evidence of brain-stem function (Stockard et al. 1977, 1980). This obvious lack of major effects of sedative drugs on SSEPs and BAEPs may account for the little interest payed to recording these potentials in drug poisoned comatose patients. In this paper a preliminary report on SSEP and BAEP findings in 5 patients in coma due to a depressant drug overdose is given.

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Methods

SSEPs were elicited by stimulation of the median nerve at the wrist and recorded with tin/lead electrodes placed over the 7th cervical vertebra and over the central area of the scalp contralateral to the stimulated wrist. The technical data were the same as in a previous publication (Rumpl et al. 1983). The differences in peak latency between N13 and N20, the CCT and the amplitude ratio (AR) between the peak of N20 and subsequent positivity (P20 or P25) and the peak of N13 and subsequent positivity were measured in millimeters and calculated for each side.

Click signals (0.1 msec pulses of alternating polarity) were presented monaurally at an intensity of 90 dB HL at a rate of 10/sec. The BAEPs were recorded from the ipsilateral and contralateral ear (vertex-mastoid derivation) for better identification of wave V (Stockard et al. 1978a). The responses were amplified 10^5 passed through a 150–3200 Hz filter and were averaged and re-

TABLE I

Mean central somatosensory conduction time (CCT) and amplitude ratios (AR from SSEPs and mean interpeak latencies (IPLs)) from BAEPs studied in 22 normal subjects. The mean age is 27 years, varying from 18 to 52 years. Right and left indicate electrical right or left median nerve stimulation or alternating click stimulation of the right or left ear (BAEP). The amplitude relationships of wave N20 : N13, and of wave I : V or I : IV/V are expressed as ratios. In order to arrive at this mathematical relationship the heights in millimeters are used.

SSEP	CCT (msec)		AR	
	Right	Left	Right	Left
Mean	5.7	5.8	1.2	1.0
S.D.	0.4	0.5	0.6	0.6

BAEP	IPLs						ARs			
	I–III (msec)		III–V (msec)		I–V (msec)		I : V		I : IV/V	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
Mean	2.1	2.1	1.8	1.8	4.0	4.0	0.6	0.6	0.5	0.6
S.D.	0.12	0.17	0.16	0.10	0.18	0.20	0.2	0.2	0.1	0.1

corded over a 12 msec time base. Two series of 1024 clicks were averaged.

Calculations performed included the interpeak latencies (IPLs I–III, III–V, I–V) and the amplitude ratios (ARs, I : V, I : IV/V). For calculation of these ARs the peak of wave I and subsequent negativity, and the peak of wave V or the highest point of the wave IV/V complex and subsequent negativity were measured and then divided. Normal data for both tests are listed in Table I.

Patients and results

For this study 5 patients after ingestion of sedative drugs with suicidal intent were investigated. None of our patients appeared cold and rectal temperatures were normal (36.2–37.5 °C) at the time of EP testing. Clinical examination disclosed flaccid coma with absent reaction to pain in all cases. Respiration had to be sustained by controlled (cases 1,2 and 4) or assisted ventilation (cases 3 and 5). Pupillary reactions were preserved in cases 1, 3, 4 and 5, but absent in case 2. The oculo-cephalic and corneal reflexes were absent in all patients. Cases 1, 3, 4 and 5 were treated by forced diuresis in case 2 dialysis of the blood by means of an artificial kidney was performed.

Case 1

This female patient aged 58 years took an overdose of barbiturates in combination with alcohol. A qualitative analysis of the blood revealed toxic amounts of cyclobarbital and its metabolites. The patient was alert within 16 h.

On admission CCT after right and left median nerve stimulation was remarkable increased (9.0 msec each). N20 showed a bilateral double peak configuration demonstrating a positive/negative wave on the descending part of N20. There was no difference of significance between the two responses, the ARs were within the range of normals.

Case 2

This 42-year-old female patient took an overdose of amitriptyline. Within 4 h the pupils started to react to light, 12 h later the patient was alert without any neurological deficit.

At the start of recording both CCTs were markedly increased and showed a clear asymmetry (Fig. 1). There were little changes in CCTs within the first 2 h. Thereafter both CCTs decreased. Plasma concentration of amitriptyline was elevated (level of fatal overdose), further increased and finally decreased to lower but still toxic level of amitriptyline (Fig. 1). At the first test, there was a

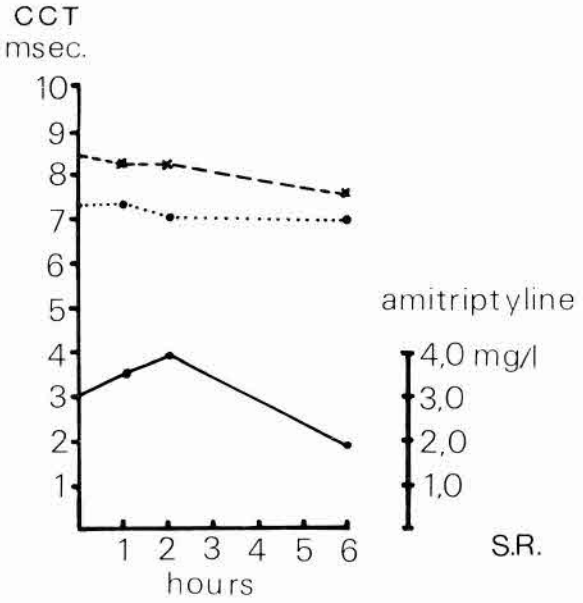

Fig. 1. The course of CCT and of the plasma level of amitriptyline in case 2 (42-year-old female patient after intake of an overdose of amitriptyline); toxic levels of amitriptyline were related to markedly prolonged CCTs; clear differences in CCT after right median nerve stimulation (dashed line) and after left median nerve stimulation (dotted line). There is a decrease of both CCTs, but CCTs were still prolonged at lowered but still toxic levels of amitriptyline 6 h later.

double peak configuration of N20 on the left hemisphere. N20 turned to a better shape and amplitude during the course of coma. Thereby the ARs slightly increased (Fig. 2a–d).

Case 3

This 54-year-old female patient made a suicidal attempt with an overdose of meprobamate combined with secobarbital. After 1 h muscle activity in the neck increased and a shivering myoclonus in all muscles appeared. After 6 h the patient was drowsy and after 10 h she was alert and demonstrated no neurological deficit.

On admission the first SSEP records revealed a markedly prolonged CCT after right (10.5 msec) but also after left (7.8 msec) median nerve stimulation. BAEPs showed normal responses in regard to amplitude, but IPLs were clearly increased after right ear (I–III = 2.2, III–V = 2.2, I–V = 4.4 msec) and after left ear (I–III = 2.3, III–V = 2.2, I–V = 4.5 msec) stimulation. One hour later the CCTs decreased (8.7 msec after right, 6.8 msec after left stimulation). The ARs were unchanged in left scalp SSEP records (0.4) but increased on the right (0.5–0.7). At that time an unacceptable level of muscle artifacts prevented the recording of useful BAEPs.

Case 4

This 27-year-old male patient took an overdose of amitriptyline. Eleven hours after admission (at the time of the fifth EP recording) the neurological examination revealed a flaccid posture, but painful stimuli evoked weak decerebrate posturing. Spontaneous respiration was sufficient. Thirty-four hours after admission (10 h after the latest EP recording) the patient was alert.

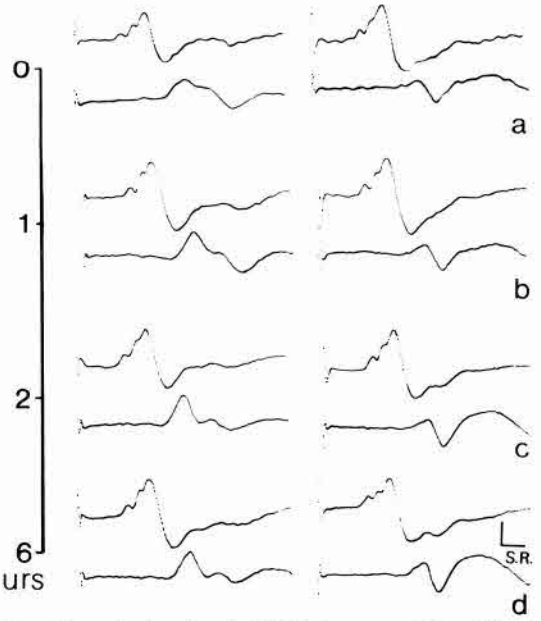

Fig. 2. a–d: cervical and scalp SSEPs from case 2 (see Fig. 1) recorded 4 times during the course of coma; flaccid coma with non-reacting pupils at the time of first 3 tests, at the last test slight pupillary reaction to light; first 3 tests done each hour (a–c), 4 h between test 3 and test 4 (time table on the left side). Note the significant side differences in wave form and CCT, which gradually disappeared during the course of coma; double peak configuration of N20 on the left changed to a better shape, the ARs generally increased. Responses after right median nerve stimulation are seen on the left, after left stimulation on the right. Calibration: 1.25 μV and 5 msec.

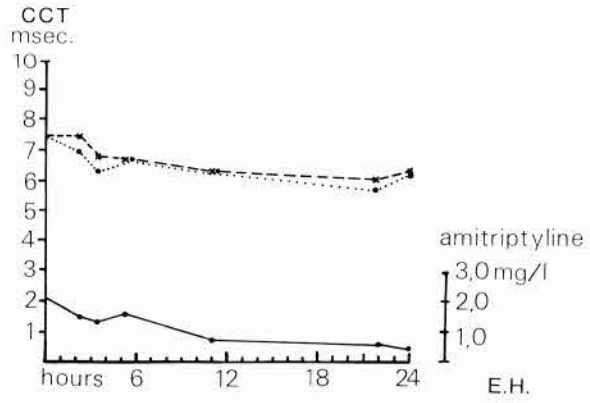

Fig. 3. The course of CCT related to plasma levels of amitriptyline in case 4 (24-year-old male patient after intake of an overdose of amitriptyline, first suicide attempt); the toxic level of amitriptyline showed some fluctuations, which were related to changes in CCT. Continuous decrease of CCT and amitriptyline; slight increase of CCT at the last test despite further fall of amitriptyline to therapeutic plasma level; only slight differences after right (dashed line) and left (dotted line) median nerve stimulation.

On admission both CCTs slightly increased (Fig. 3). The BAEPs demonstrated markedly increased IPLs after right (I–III = 2.6, III–V = 2.4) and after left ear (I–III = 2.7, III–V = 2.4) stimulation (Fig. 4). CCTs and IPLs decreased during the next 22 h. There was a corresponding decrease of amitriptyline from a toxic to a therapeutic plasma concentration (Figs. 3 and 4). The last test showed CCTs and IPLs slightly increased, despite a further decrease of amitriptyline. The IPLs I–III

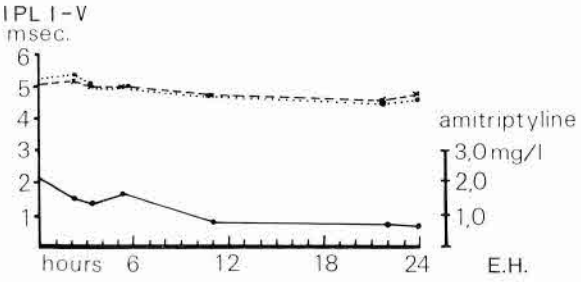

Fig. 4. The course of IPL I–V related to plasma levels of amitriptyline in the same patient as in Fig. 3; same time of testing as in Fig. 3; slight increase of IPL in the beginning, but afterwards decrease of IPL following decrease of plasma amitriptyline level; finally, slight increase of IPL despite further decrease of amitriptyline. Broken lines mark IPL after right ear, dotted lines mark IPL after left ear stimulation.

were little changed during the course of coma, but a marked decrease of IPLs III–V (2.0 msec after right, 1.9 msec after left ear stimulation) resulted

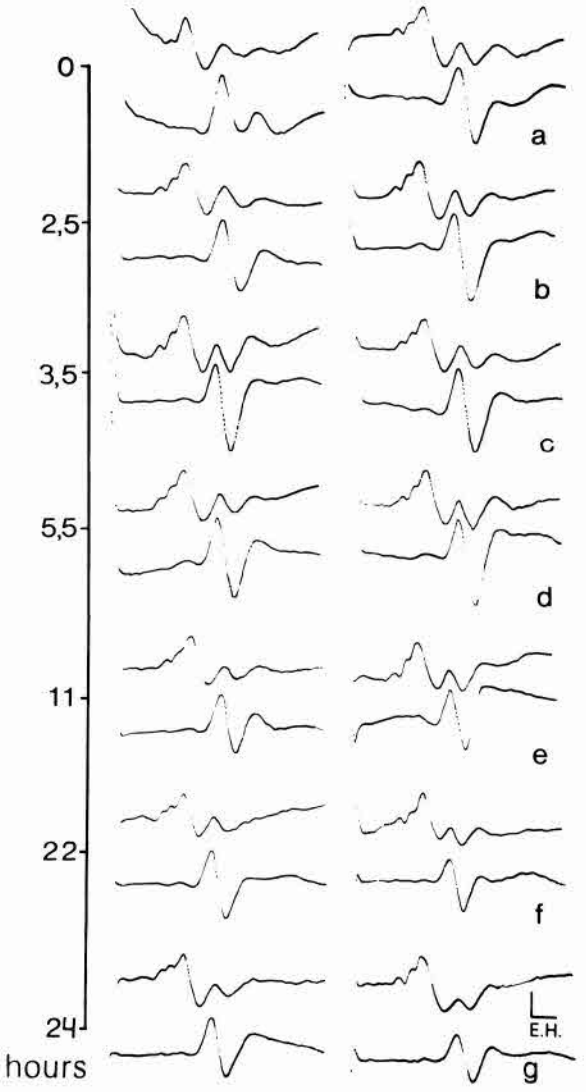

Fig. 5. a–g: follow-up records of cervical and scalp SSEPs from case 4 (see Fig. 3); first suicide attempt; toxic amounts of plasma amitriptyline; flaccid coma with poorly reacting pupils; total time of observation 24 h; time intervals between the tests marked on the left side. Note better shape of N20 on the left hemisphere in the second test and increase of amplitude of N20 till test d; thereafter slight decrease of amplitudes of N20; CCT continuously decreased, but increased slightly in the last test; N20 always well defined. Side of responses as in Fig. 2. Calibration: 0.63 μV and 5 msec.

in a clear reduction of IPL I–V. The SSEPs demonstrated asymmetry of wave form, showing double peak configuration after right median nerve stimulation. The ARs always were within the range of normal but showed a slight increase within the first and a slight decrease within the last hours of observation (Fig. 5a–g). The asymmetry of SSEP responses between the hemispheres disappeared. The ARs I : V slightly increased during the first 5 h, slightly decreased in the next 19 h. These ARs were within the range of normal too (Fig. 6a–g).

Sixteen days after the first suicide the patient repeated his attempt using amitriptyline again. Fourteen hours after admission he started to move extremities. A further 12 h later he was alert.

After the patient's second suicide attempt EP recording was first done 10 h after admission. At the time CCT was slightly prolonged after right median nerve (7.0 msec) but was normal after left median nerve stimulation (6.3 msec).

Within 5 h both CCTs decreased (6.5, 5.8 msec, respectively). The ARs were normal in the first test, then slightly increased. The IPLs I–V showed a weak reduction from 4.6 msec each to 4.5 and 4.4 msec respectively. This reduction was mainly caused by reduction of IPLs III–V. The ARs I : V showed minor changes. Plasma concentration of amitriptyline was within the therapeutic plasma level at each test varying from 0.8 mg/l to 0.1 mg/l (last test).

Case 5

This 79-year-old female patient made a suicidal attempt with an overdose of nitrazepam. A quality analysis of the blood demonstrated remarkable amounts of nitrazepam. Two days after start of treatment the patient was alert, but showed unilateral neurological deficits (left hemiparesis, left central facial nerve deficit). Within 24 h she recovered from her neurological troubles, which were thought to be due to a transient ischemic stroke. At the time a CT scan of the head and the EEG revealed normal findings.

Two hours after admission SSEP recording demonstrated CCTs within the range of normals after right and left median nerve stimulation. However, there was a difference of CCT after right (5.8 msec) and after left (6.5 msec) stimulation. The ARs showed poor difference (2.0, 1.8 respectively). The main negative deflection N20 and the following waves showed a weak double peak on both sides. The amplitude of the neck response (N13) was small. The IPLs I–V were 4.2

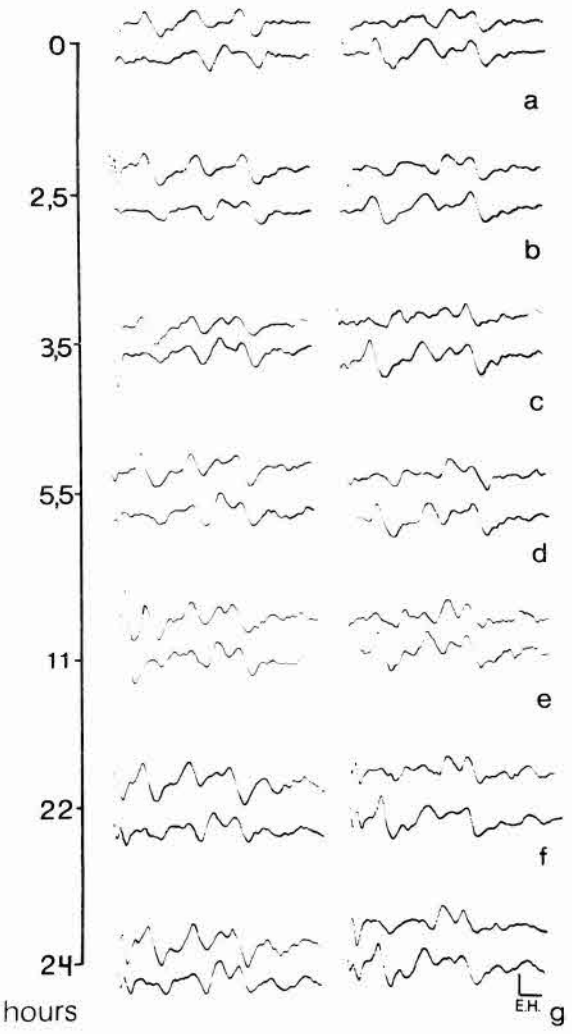

Fig. 6. a–g: follow-up records of BAEPs from the same patient as in Fig. 3. BAEPs were recorded immediately after SSEP tests. Note the increasingly better wave IV/V complex with lowering of overdose; the IPL I–V continuously decreased, but similar to CCT increased at the last test; all waves well formed during the course of coma. Bilateral derivation for better identification of wave IV/V complex, right ear stimulation on the left, left ear stimulation on the right side. Time intervals as in Fig. 3. Calibrations: 0.15 μV and 1.2 msec.

msec after right, 4.1 msec after left ear stimulation (I–III = 2.4, III–V = 1.8, I–III = 2.2, III–V = 1.9 respectively). The ARs I : V were 0.3 and 0.4 respectively.

Discussion

Studying 9 patients in coma due to a drug overdose (including barbiturates, diazepam, amitriptyline), Starr and Achor (1975) found BAEPs usually normal with regard to latency and amplitude of all components. In contrast, Sutton et al. (1982) reported increases of IPLs in a limited number of human subjects in deep barbiturate coma. Similarly, Hume and Cant (1981) reported a direct correlation of CCT with serum phenobarbital levels in a study of head-injured patients, but the combined effects of drug and body temperature contributed of only 4% of the variance in CCT. A delay of CCT was also observed during deep barbiturate anesthesia in experimental animals, but not in light anesthesia (Shaw and Cant 1981).

All our patients were deeply comatose (flaccid coma). Our cases 1, 2, 3 and 4 (first suicide attempt) had strongly delayed CCTs and IPLs. Follow-up examinations showed that CCT and IPL tended to normalize, even when the clinical condition had not changed (cases 2, 3 and 4). Case 4 (in his second suicide attempt) and case 5 had normal CCTs. From these observations one might suggest that there are two coma levels of CNS depressant drugs. First, a 'toxic' coma level with prolonged CCTs and IPLs a second, a 'therapeutic' coma level with normal CCTs and IPLs. This suggestion might be further supported by the results of monitoring the plasma concentration of amitriptyline in our cases 2 and 4, who both had prolonged CCTs corresponding to toxic levels of amitriptyline. In these cases the plasma concentration of amitriptyline was at the level of fatal overdose (Baselt 1982).

Further support came from the findings in our case 4 during his second suicide attempt, when he used the same drug. Despite flaccid coma the plasma concentration of amitriptyline was within the therapeutic range. The corresponding CCTs were normal. Once the patients had normal CCTs they were usually alert within a few hours. In contrast to the normalization of CCT the IPL I–V appeared to be longer affected. Delayed IPLs I–V were found in case 4 (first and second attempts) despite normal CCTs. However, latencies of CCT and IPL were generally closely related and increased and decreased together. Normal CCTs and IPLs were found in our case 5 who made a fast recovery.

The hypothesis of a 'toxic' and a 'therapeutic' coma level may also explain the discrepancy of severely delayed SSEPs and BAEPs in our cases and the generally accepted suggestion that latencies of SSEPs and BAEPs are not significantly affected by sedative drugs and anesthetics (Chiappa 1983a,b; Grundy 1983). It appeared from previous reports and our findings that changes in latencies of SSEPs and BAEPs are dose-related events, which only appear in the case of severe overdose.

The exact mode of action of amitriptyline is unknown, but the drug may block the uptake of amine neurotransmitter released into the synaptic cleft. Further it is generally believed that the synapse is the site of action of hypnotic compounds (Sharpless 1970). Although their neurophysiological basis is not necessarily similar, their sedative effects in overdose may be comparable. In our cases, N13 appeared to be rather constant in wave form and latency but N20 was increasingly delayed. This finding may demonstrate that the synaptic attenuation predominantly involved thalamic and cortical structures (Hume and Purkin 1986). Slowing of transmission at the synapse may also account for temporal dispersion and lessening of amplitude of N20 (double peak configuration), which both disappeared with lowering of intoxication. In comparison to CCTs the ARs were less remarkably altered in our cases. They slightly increased within the first hours and showed little changes in the further course of intoxication. Since increase of CCT combined with increases in amplitudes may be caused by slowing of axonal conduction this mechanism of action may also be involved in toxic coma levels (Markand et al. 1984). Similarly, the BAEPs showed little changes in ARs. The ARs I : V varied within the course of

coma (case 4, first and second suicide attempts), but wave V and the wave IV/V complex were always well defined and no significant decrease in amplitudes was noted. Interestingly, the IPLs I–III were more strongly delayed than IPLs III–V. It further appeared from our findings that IPLs I–III were still prolonged, even when the IPLs III–V had normalized. Considering that wave II might be generated in the extramedullary portion of the eighth nerve (Stockard et al. 1980; Goldie et al. 1981; Garg et al. 1982), the depressive effects on neuronal function may act more strongly on generators sited extramedullary. The rather constant amplitudes of spinal and scalp SSEPs, as well as BAEPs, made it unlikely that hypothermia had an important impact in our cases. Decreases in amplitude of both SSEPs and BAEPs were found to be characteristic for hypothermia (Stockard et al. 1978b; Budnick et al. 1981; Hume and Purkin 1986).

Since side differences in CCT and wave form are not mentioned at all in the literature during general anesthesia and therapeutic barbiturate coma (Grundy 1983; Stockard and Iragui 1984), this might be a peculiar finding in our patients with severe drug overdose. In all our cases asymmetries of CCT disappeared or clearly diminished during the course of coma. Such an asymmetric CCT may be seen as an index of ischemia and a sensitive monitor for hemispheric dysfunction prior to the onset of the clinical deficit (Symon et al. 1979). The prolonged and asymmetric CCT in cases 2, 3 and 4, in which a clinical deficit was not apparent, might have indicated an early warning of ischemic deficit which indeed in case 5 subsequently appeared. No difference of significance was seen in BAEPs after right and left ear stimulation.

Since all of our patients had good recovery, it appeared that prolonged CCTs and IPLs and also the dispersion of N20 had no prognostic significance. Increase of CCT and IPL pointed to severe intoxication but not to a bad outcome. Considering our findings in posttraumatic coma, where the combination of prolonged CCT or IPL with low ARs usually pointed to severe disability or death (Karnaze et al. 1982; Rumpl et al. 1983), one might speculate that depressions of the ARs combined with prolonged CCT and IPL would be a more serious sign. In BAEPs the suppression in amplitude of wave III to wave V was already demonstrated in animals at increasing levels of pentobarbital concentrations (Sutton et al. 1982).

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Abstract

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