

Recommendations from the Clinical Toxicology Committee of the Society for Toxicological and Forensic Chemistry (GTFCh) for toxicological analysis in the context of determining brain death.

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1. Recommendations

It is not the duty of the GTFCh to define the pharmacologically substantiated decision limit for judging the concentrations of narcotising substances. However, it is necessary to:-

1. use the lower limits of the therapeutic range with standardised concentration values in mg/L,
2. relate the lower limit of the measuring range to this, and
3. establish quality criteria for the analysis.

The demands on a qualitatively specific and quantitatively reliable analysis are only met by the use of chromatographic techniques with high identification power (e.g. HPLC-DAD, LC-MS or GC-MS). The methods used should be validated. By way of internal and external quality assurance, the comparability of the results should be attained and documented.

At present, lower measuring range limits are recommended for the active substances named in table 1. This means that quantitative values below the measuring range limits can neither be acquired nor judged. For the lower limit of concentration values (lower limit of measuring range), half of the lower limit of the therapeutic range is recommended.

The latter were defined by taking several pharmacological / toxicological data pools [1-5] in table 1 into account. When disclosing the findings, generally acknowledged criteria should be applied [6]. The interpretation of the findings must be performed by the doctors responsible for brain death diagnostics and, if need be, together with experienced toxicologists.

Table 1: Details relating to the therapeutic range and measuring range of relevant active substances

Active substance	Lower limit of therapeutic range (mg/L)	Recommended lower limit of measuring range (mg/L)
Thiopental	1.0	0.5
Pentobarbital		
(Thiopental metabolite)	1.0	0.5
Phenobarbital	10.0	5.0
Methohexital	0.5	0.25
Midazolam	0.04	0.02
Diazepam	0.2	0.1
Nordazepam		
(Diazepam metabolite)	0.2	0.1

2. Justification

2.1. General

Brain death is defined as the state of total irreversible loss of function of the cerebrum, cerebellum and brain stem. Brain death describes, scientifically and medically, human death [7].

The diagnosis of brain death requires:-

1. The fulfilment of the prerequisites (see section 2.2)
2. The determination of the clinical symptoms:- coma, brain-stem areflexia and apnoea
3. Proof of the irreversibility of the clinical failure symptoms

Brain death can be determined in every intensive care unit, even without supplementary machine-aided diagnosis, except for children under 2 years old and in cases of primary infratentorial brain damage. If the doctor observes a sure external sign of death, then this is also proof of brain death. According to Article 16, Section 1 of the German law governing transplantation, the “Guidelines for Determining Brain Death” are binding. They describe in paragraph 2 how the significance of central nervous system depressants can be judged, given the failure symptoms in the period of examination. Here, in agreement with other recommendations [8,9], none of the active substance concentrations which rule out or allow the determination of brain death are named or even specified. This is due to the fact that at present, concerning the acute severe primary or secondary brain damage leading to brain death, no reliable concentration-effect relationship exists for most CNS depressants to be able to judge the influence of medication on certain findings. In spite of this, it is clinically very helpful in the frame of checking the prerequisites for brain death, if toxicological investigations are performed not only to rule out intoxication, but also to check for the therapeutic use of centrally acting medication.

2.2. Diagnostic Prerequisites for Determining Brain Death according to the Guidelines of the BÄK (German Federal Council of Doctors) (Dt. Ärztebl 95, A1861-A1868, 1998)

Prerequisites:

- Existence of acute severe primary or secondary brain damage
- Exclusion of **Intoxication**
- Exclusion of **depressant effects of medication**
- Exclusion of a neuromuscular blockade
- Exclusion of primary hypothermia
- Exclusion of circulatory shock
- Exclusion of an endocrinal, metabolic or inflammatory-based coma

Limiting prerequisites:

Through the history of the case and the findings, it must be guaranteed that none of the above causes are responsible for the failure symptoms at the time of the examination. The significance of central nervous system depressant medication regarding the failure symptoms can be judged by the:-

- association of medication already administered with the findings,
- effects of antidotes
- neurophysiological findings not able to be suppressed by medication
- examination of blood supply to the brain

For the brain damage discussed here, no reliable concentration-effect relationship exists for most of the central nervous system depressant medication to be able to judge its role in certain findings.

In case of doubt, cerebral circulatory standstill must be proved within the frame of brain diagnostics.

2.3. Significance of the Toxicological Analysis for the Determination of Brain Death

According to the views of the US Americans pursuant to the *Uniform Determination of Death Act*, brain death can be determined even if the concentration of the narcotising medication administered is below the therapeutic range [10]: *There is a clear difference between severe brain damage and brain death with complete irreversible loss of brain stem function. A more complex problem is the possible confounding of the clinical determination of brain death by metabolites or traces of circulating pharmaceutical agents. Screening tests may be helpful. A clinical diagnosis of brain death should be allowed if drug levels are below the therapeutic range. Or the patient should be observed for a period that is at least four times the elimination half-life.* "Half-life" is understood here as the terminal elimination half-life after cumulative dosage. For toxicological examinations before establishing brain death (checking of the prerequisites), no special guidelines exist to date. Standardisation of the methods for the qualitative and quantitative analysis and recommendations concerning the lower measuring range limits are desired by the initiator of the enquiry as help in the efforts to create uniformity and credibility when the practitioner is in an awkward situation.

For this reason the aforementioned recommendations were developed for the field of toxicological analysis. These are intended to lead to unification of both the analytical quality criteria and the disclosure of the findings.

3. References

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