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Barbiturate Narcosis in Neuro-Intensive Care .

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Abstract

As it stands now, in the pharmaco-therapy of cerebral resuscitation, short acting barbiturates (thiopentone, pentobarbitone) are the only two drugs which seem to have some selective clinical applicability. In the management of severe head injury patients (Glasgow coma score < 7) there is ample clinical evidence to suggest that barbiturate therapy may be of help in controlling the ICP, in a select group of patients ("uncontrolled ICP") [14]. The suggested dose schedule for pentobarbitione therapy would be 5-10 mg/kg bolus followed by 1-3mg/kg/hour infusion. The desired level of plasma barbiturate would be 2-4mg%. The various criteria which would guide in titrating the therapy are-desired end point of therapy (control of ICP, control of convulsions), plasma barbiturate level, EEG burst suppression etc. Continuous monitoring of cardio-vascular parameters like mean arterial pressure, cardiac-index, pulmonary artery wedge pressure etc is very essential. Attention is drawn to the response of a patient to barbiturate therapy and its relation to response to change in PaCO2.

Key words -

Barbiturate narcosis,
Mangement,
Brain protection,
Brain resuscitation,
Severe head injury

In resuscitation science, the 1950's was devoted to respiratory resuscitation, the 1960's to cardiac resuscitation and 1970's to cerebral resuscitation. Cerebral resuscitation has been the focus of attention of both the basic scientists and clinicians for the last two decades. This is an area where clinicians from several specialties have pooled their wisdom and worked towards a common goal. Anaesthesiologists are basically interested in global cerebral ischemia (post cardiac arrest cases). Neurologists in focal cerebral ischemia (stroke) and the Neurosurgeons in the applicability of cerebral resuscitation in severe head injuries.

In the pharmacotherapy of cerebral resuscitation, the potential resuscitative value of several drugs have been extensively evaluated. Among the drugs which have been studied are [1], [2], [3]

-Barbiturates
-Calcium channel blockers
-Gama aminobutyric acid

-Glutamate aspartate antagonists
-Prostaglandin inhibitors etc.

Though several drugs have been evaluated, as of now, with barbiturates there is adequate laboratory as well as clinical evidence, to justify their use in clinical practice, in select group of patients. Several experiments have been carried out to study the role of barbiturates in experimental global ischemia [4], [5], [6]. The consensus is, barbiturates have no role in global ischemia [7], [8]. The clinical trial of Abramson et al [9] (role of barbiturate coma in post cardiac arrest cases) also showed that barbiturate narcosis is of no additional benefit, over and above the standard intensive care measures. In focal ischemia (stroke) though several animal studies have clearly demonstrated the therapeutic role of barbiturate coma [10], [11], there is as yet no clinical data to support this. In severe head injuries [12] (Glasgow Coma Score < 7). as a last resort for controlling the ICP in patients with "uncontrolled rise in ICP", it is probably does have a role (literature discussed below).

As per one f the reports, in USA & UK, in almost 50% of the neuro intensive care units, barbiturate narcosis is routinely practiced- as a form of therapy-predominantly in severe head injury cases (personal communication Dr. A. H. Ropper and Dr. J. D. Miller). Keeping this in view, the rest of this review will be devoted to the role of barbiturate narcosis in severe head injuries and clinical management of barbiturate narcosis. The standard management protocol followed in severe head injuries (aggressive line of management) [13] is as shown in Table I. This includes early and prompt resuscitation of the patient (at the site of the accident) and prompt transportation to a head injury care centre. In the hospital, patient should be investigated to rule out any treatable mass lesion - which if present, calls for early surgical decompression of the lesion.

Table I - Severe head injury (management protocol)

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Once this is done, rest of the management is directed towards monitoring and maintaining the ICP within the normal range. A patient who does not respond to the standard measures of ICP control like-

- Position
- Hyperventilation
- Hyperosmolar therapy
- CSF drainage
- Paralysis / sedation,

is one who comes under the category of "uncontrolled ICP" [14]. These are the patients who should be considered for barbiturate narcosis. Only 15-25% [15], [16] (often less) of all severe head injury patients, come under this category of uncontrolled ICP. Mortality in these patients is said to be very high, in the range of 84-100% [17], [18], [19], [20].

Recently there have been three clinical control trials, on the role of barbiturate narcosis in severe head injury patients. In Schwartz et al's [21] study it was a comparison of pentobarbitone vs mannitol for ICP control. In Ward et al's [22] study, role of prophylactic barbiturate coma was compared with conventional ICP control measures. In both these studies, the authors have concluded that barbiturate therapy should be reserved for patients with uncontrolled intracranial pressure (patients who do not respond to the standard ICP control measures). This, incidentally, was the protocol followed in the third study reported by Eisenberg et al [23]. This was a collaborative multi-institutional study done in the U.S.A. Out of 925 cases of severe head injury, only 116 (12.5%) of them had uncontrolled ICP. Of these 116 patients, only 73 patients were randomized for the clinical trial, 36 patients in the control group received conventional ICP control measures (Table I) while 37 patients in the treatment group received pentobarbitione in addition to the conventional ICP control measures. Percentage of patients with ICP control was double in the treatment group (33% -out of 37 patients) as compared to only 16% out of 36 patients, in the control group. The authors have not commented about the mortality, because of ethical consideration.

Management of barbiturate narcosis

Pentobarbitione and thiopentone are the two drugs which have been most commonly used. Pentobarbitone has been used more frequently probably because it has a slower onset of action and hence can be given intermittently. Thiopentone, on the other hand, has a faster onset of action and hence has to be given as an infusion. Aside this, neither of them have any therapeutic advantage over the other.

Monitoring

The various physiological parameters to be monitored (essential and desirable) are listed in Table II. For ICP monitoring, intraventricular monitoring is preferable- as this permits letting out of CSF. Arterial pressure should be monitored continuously and a mean arterial pressure of more than 90 mm of Hg should be maintained. In order to ensure adequate preload to the heart, pulmonary artery wedge pressure should be maintained within normal limits (10-14 mm/Hg). It would be desirable to monitor end tidal CO2 and EEG also.

Table II - Monitoring during barbiturate narcosis

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Dose

No rigid dose schedule can be recommended, as it varies depending on the indication for therapy, response of the patient and end point of therapy desired. Desired end point of therapy in turn depends on the primary indication - as in head injuries it is control of ICP and in status epilepticus, it is control of convulsions. Certain other guidelines for adjusting the dosage are-

i) Blood level of barbiturate -if it exceeds 4-4.5 mg%, the chances of complications are more.

ii) EEG-once the EEG becomes isoelectric, there is no therapeutic advantage in giving more drug.

iii) Acute side effects, like hypotension.

Table III - Dose of pentobarbitone

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In the three clinical studies, cited earlier the dose of pentobarbitone used was more or less the same (Table III). Hence as a guideline pentobarbitione dose of 5-10 mg/kg bolus, followed by 1-3 mg / kg / hour as a continuous infusion, aiming at a blood level of 2-4 mg %, is recommended. Acute tolerance has been reported during barbiturate therapy. Sawada et al [24] infused thiamylal to severe head injury patients, for 72 hours, to induce and maintain EEG burst suppression. They observed that the plasma level of the drug required to maintain EEG burst suppression more than doubled over the course of 72 hours (from 2.05 ± 0.58 to 4.82 ± 0.63 mg %). However the total dose of the drug required per day remained the same. Further, it has been reported that, though the therapeutic blood level increased, toxic level of the drug does not rise simultaneously. This indicates that plasma level of the drug alone as a guideline would be inadequate. The practical end points of therapy, suggested are as follows-

- If ICP is controlled, maintain the therapy for 48-72 hours and then taper it off.
- If ICP is not controlled and if arterial pressure is stable, increase the dose of the drug.
- If ICP is not controlled, and arterial pressure is low, supportive measures for arterial pressure control

like, fluids, dopamine infusion etc. should be instituted.
- Inspite of maximum cardiovascular support if arterial pressure is still low, reduce the dose of the drug.
- If ICP is not controlled and EEG is isoelectric, there is no advantage in giving more drug. Hence no alteration in dose schedule is warranted. The dose may, if necessary be slightly reduced, so as to maintain EEG burst suppression.

Response of a patient to barbiturate narcosis

Messeter et al [25] and subsequently Nordstrom et al [26] have reported that in severe head injury patients, response to barbiturate narcosis, is related to cerebral vasoreactivity of the patient to change in PaCO2. Patients with preserved vasoreactivity responded with a substantial decrease in CBF and ICP in response to barbiturate narcosis. In such patients, the outcome was also good. In patients with impaired cerebral vasoreactivity to PaCO2, barbiturate narcosis causes no change and may even cause a rise in CBF. In such patients, as anticipated, outcome was poor. The relationship between CBL vasoreactivity and response to barbiturate narcosis is depicted in Table IV. The normal CBL vasoreactivity to PACO2 (CBF / PaCO2) is 2.2 ± 0.6 units. Patients with a vasoreactivity of > 1.0 unit, have a normal response to barbiturate narcosis ((CBF and (ICP). Patients with a vasoreactivity of >1.0 unit, have an impaired response to barbiturate narcosis (no change in CBF or increase in CBF).

Table IV - CBL vasoreactivity to PaCO2 vs response to barbiturate narcosis

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Haemodynamic response

Haemodynamics of patients, during and following barbiturate narcosis has been studied by Todd et al [27], [28]. In two different clinical studies, one with pentobarbitone and the other with thiopentone, sufficient dose of thiopentone was infused to achieve EEG burst suppression and haemodynamic parameters were studied. The study was carried out in patients posted for elective neurosurgical procedure and in order to avoid the influence of surgical stimuli, study was done prior to endotracheal intubation and start of surgery, for a period of 30 minutes. It was observed that, following barbiturate narcosis, all patients had evidence of myocardial depression, as indicated by a decrease in stroke volume index, which was compensated for by a rise in heart rate, thus maintaining the cardiac index within normal range. Systemic arterial pressure also decreased, with a resultant decrease in mean arterial pressure. Pulmonary artery wedge pressure was maintained within normal limits (10-14 mm/Hg) by infusing 1-2 litres of ringer lactate (in order to avoid the influence of relative or absolute hypovolemia). The dose of thiopentone required, was double as compared to the dose of pentobarbitone. Todd et al recommended that normal pulmonary artery wedge pressure should be maintained during barbiturate narcosis.

Traegar et al [29] studied the hemodynamics of 5 severely head injured patients, who were given pentobarbitone (7 mg/kg bolus, 1-3 mg/kg intermittently) to achieve EEG burst suppression. The

authors concluded that, increase in venous capacitance, hypovolemia and decrease in barostatic reflexes, rather than depression of myocardial function, accounted for the haemodynamic abnormalities in most patients. Further, the authors recommended that, during barbiturate narcosis, cardiovascular parameters should be monitored and maintained within normal limits (Table V).

Table V - Cardiovascular parameters

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In addition to cardiovascular imbalance (discussed above) some of the other problems likely to be encountered in a patient on barbiturate narcosis, are listed in Table VI. Hypothermia occurs because barbiturates cause peripheral vasodilatation, which in turn causes heat loss from the body. Patients on barbiturate narcosis are prone for pulmonary as well as systemic infections. This could be due to many factors like suppressed immune response of the body (likely to occur during barbiturate coma), prolonged immobilisation, invasive form of monitoring required etc.

Table VI - Other complications during barbiturate narcosis

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Evaluation of the present state of barbiturate narcosis shows that the one situation where it may still have a role, is in the management of uncontrolled ICP, in severe head injuries (Glasgow Coma Score < 7). Barbiturate narcosis is a difficult therapeutic procedure and needs extensive monitoring and intensive care management. But with proper attention to factors such as intravascular volume, dosage of the drug etc. even very large doses of barbiturates can be given safely, to patients who do not have any associated systemic abnormality.

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