FURTHER EXPERIENCE WITH DIAZEPAM (Calmpose®) IN ECLAMPSIA*

by
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Introduction

In view of certain practical difficulties associated with the conventional treatment of eclampsia with lytic cocktail and the documented evidence of extreme usefulness and safety of diazepam in various convulsive disorders (Shershin et al, 1964; Femi Pearse, 1966; Howard et al, 1968; Dundee et al, 1970), diazepam was thought worthy of trial in eclampsia. Diazepam is a derivative of benzodiazepine group of drugs, which exhibits hypnotic, muscle relaxant, and anticonvulsant effect without depressing the vital centers. Thus, we started using diazepam in the management of eclampsia in our hospital since October 1971. The preliminary findings were encouraging (Kawathekar et al, 1973). The trial has since been completed and this report summarizes our findings.

Patients and Method

Thirty cases of eclampsia were treated in the obstetric department of M. R. Medical College and Government General Hospital, Gulbarga from October 1971 to December 1973. Diazepam 40 mg. diluted in 10 ml. of 5% dextrose was given as soon as the patient was admitted and an infusion of 40 mg. diazepam in 5% glucose was started simultaneously. Diazepam was repeated every 4-6 hours in 20-40 mg. doses intravenously through the tube; parenteral therapy was continued till 24 hours after delivery, and thereafter orally in 10 mg. doses every 6th hourly for one week.

Diuretics

Intravenous Frusemide 40 mg. was given on admission and thereafter orally for one week.

Hypotensive drugs

Additional hypotensive drugs in the form of methyl dopa in 2 cases and reserpine in 2 cases were given to control the blood pressure.

General Management

Important information like age, parity, number of convulsions, duration of pregnancy was obtained from the relatives of the patient. Observations were recorded frequently on a specially prepared proforma to enable us to study the effect of diazepam on the vital signs, urine output and grades of unconsciousness. Routine urine analysis, haemoglobin estimation, and optic fundus examination were carried out in all the cases and repeated whenever necessary.

Obstetric Management

Obstetrical examination was made at the end of one hour when the patient was
fully sedated, and reassessment was made at the end of 12 hours of treatment. If the cervix was effaced and 4 cms. dilated, artificial rupture of membranes was performed. Caesarean section was performed at the end of 12 hours if the cervix remained unfavourable. The progress of labour was hastened with artificial rupture of membranes and forceps wherever necessary. Few cases delivered spontaneously. Apgar scoring was carried out in all the babies born alive.

Observations

It was observed that eclampsia is a disease of young and primigravidas as 16 cases were less than 20 years, 19 were primiparas, 5 secundiparas and remaining 6 multiparas. The duration of pregnancy was more than 36 weeks in 11 cases and less than 36 in 19 cases. Antepartum eclampsia was seen in 22 patients and postpartum eclampsia in 8 patients. The maximum number of convulsions almost like status eclampticus were infrequent, being observed only in 2 cases. Twelve cases had received sedative treatment with chlorpromazine, pethidine, mor phine, paraldehyde and phenargan, either in combination or singly before admission into our wards. The effects of diazepam on the urine output, level of consciousness, and cessation of convulsions are tabulated in Table I. There was an abrupt cessation of convulsions within 30 minutes in 26 cases and in all the cases at the end of four hours.

Recurrence of fits was noted in one case after 6 days while she was still on maintenance therapy, perhaps due to insufficient dose of the drug. The maximum blood pressure recorded at the time of starting the therapy was 206/140 and the minimum was 130/100. In 26 of the 30 cases blood pressure could be controlled adequately with diazepam sedation alone. Additional drugs like methyl dopa and reserpine were given in the remaining 4 cases. All cases were in unconscious state (Grade V, Lean et al, 1968) at the start of the therapy. The unconsciousness was maintained at lesser depths (Grade III or IV) with diazepam therapy. The maximum

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Shows the Effect of Diazepam on Convulsions, Consciousness and Urine Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEFORE DIAZEPAM</td>
<td>AFTER DIAZEPAM</td>
</tr>
<tr>
<td>Fits</td>
<td>All 30 patients. Innumerable number of fits in 2 patients.</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Grade V</td>
</tr>
<tr>
<td>Urine Output</td>
<td>Less than 30 ml in 20 patients.</td>
</tr>
<tr>
<td></td>
<td>More than 30 ml in 10 patients.</td>
</tr>
</tbody>
</table>

* Fits were controlled in all the 30 cases.
dosage of parenteral diazepam given to a case was 200 mg. and minimum was 100 mg.

The details of the nature of delivery are shown in Fig. 1. Four cases had caesarean section, 6 had delivered at home, and the remaining 20 had vaginal delivery in the hospital either aided with artificial rupture of membranes and forceps or spontaneously. The time interval between admission and delivery was between 12-28 hours.

The maternal complications like pulmonary oedema, congestive cardiac failure, deep vein thrombosis, and renal failure did not occur in the present series. Oliguria was observed in 2 patients which responded to mannitol therapy (Table II). In one patient, who had innumerable fits before starting diazepam, the incidental complication of cerebrovascular accident was noted. She had right sided hemiplegia which recovered subsequently. Even in this case convulsions could be controlled dramatically with intravenous diazepam. There was only one maternal death in our present series. This patient was admitted in coma and even though her convulsions could be controlled promptly with diazepam, she had collapsed suddenly. This death is probably not related to diazepam therapy. Although this series is small our figures are comparable to the best figures reported so far by Lean et al, 1968 and Menon, 1961 and show a remarkable decrease in the maternal mortality as compared to cases treated in our unit with lytic cocktail 1969-1971 (Fig. 2). All the babies except one who were born alive were active at birth and their Apgar scoring ranged between 7-8. The foetal prognosis appears to be better as compared to the lytic cocktail regimen (Table III).

Discussion

The efficacy of any new drug in the management of eclampsia is judged by the prompt control of convulsions, and by the safety of the drug to the mother and foetus. Absence of serious side effects and ease of administration would further enhance the value of such a drug.

Diazepam appears to fulfil these criteria very well. The convulsions were
controlled in all the cases at the end of 4 hours, in the present series, and there was only one case of recurrence of fits (3.3%). Even though the reports of the use of benzodiazepines in eclampsia are few (Gilbert, 1961; Lean et al, 1968; Elliot, 1970; Leizinger-E-Landes Frauenklin, 1970), they mention that diazepam controlled convulsions promptly and the recurrence rate was remarkably low when compared to the conventional forms of the treatment (Table IV).

### TABLE III

**Foetal Prognosis**

<table>
<thead>
<tr>
<th></th>
<th>Menon 1961</th>
<th>Lean et al, 1968</th>
<th>Our experiences with</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Lytic cocktail</td>
<td>Diazepam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1969-1971</td>
<td>(Present series)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1971-74</td>
</tr>
<tr>
<td>Total live births</td>
<td>32.1%</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Still-births</td>
<td>2</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Neonatal deaths</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Corrected perinatal mortality</td>
<td>32.1%</td>
<td>11.1%</td>
<td>33.3%</td>
</tr>
</tbody>
</table>

The exact site of action of diazepam in man is not known. However, in experimental animals it is observed to have a depressant effect on thalamus (Schallack et al, 1964) and suppressant effect on amygdala (Eidelberg et al, 1965). Thus diazepam therapy is not associated with dangerous fall in blood pressure (Katz et al, 1965) or depression of respiration (Steen et al, 1969). Sedative action is effective within minutes, yet patients do not reach higher grades of unconsciousness (Lean et al, 1968). It crosses the placental barrier rapidly but the high plasma levels do not effect foetus adversely in labour or at birth (Bepko et al, 1965; Scher et al, 1973; Mofid et al, 1973).

### TABLE IV

**Effectiveness of Benzodiazepine in Control of Convulsions as Compared with Other Regions**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drug Regimen</th>
<th>No. of cases treated</th>
<th>% of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheares 1957</td>
<td>Lytic cocktail</td>
<td>124</td>
<td>33%</td>
</tr>
<tr>
<td>Menon 1961</td>
<td>Lytic cocktail</td>
<td>402</td>
<td>15%</td>
</tr>
<tr>
<td>Gilbert 1961</td>
<td>Librium</td>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>Elliot et al 1970</td>
<td>Diazepam and Protovatertrine</td>
<td>3</td>
<td>Nil</td>
</tr>
<tr>
<td>Leinzinger 1970</td>
<td>Diazepam</td>
<td>96</td>
<td>Majority controlled</td>
</tr>
<tr>
<td>Lean et al 1968</td>
<td>Chlordiazepoxide and diazepam</td>
<td>90</td>
<td>2.2%</td>
</tr>
<tr>
<td>Present series 1971</td>
<td>Diazepam</td>
<td>30</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

In the present series all except one patient remained in grade III or IV of unconsciousness, none had respiratory depression or precipitous fall in blood pressure, and all the babies except one
born alive were active at birth. This is in marked contrast to our earlier experience with lytic cocktail regimen, where depression of vital centers of the mother and foetus posed difficult therapeutic problems.

Untoward effects

No untoward or adverse side effects were noted in the present series. However occasional atypical response in the form of cardiovascular collapse has been observed (Rollasen, 1968). Severe behaviour changes during the therapy which disappeared on discontinuing the therapy have been reported by Femli Pearse, 1966. Loss of beat to beat variation in the foetal heart rate pattern which is not associated with significant alteration in fetal pH (Scher et al, 1973) or Apgar scoring (Bepko et al, 1965) and a tendency for hypothermia (Joyce et al, 1973) in babies have been reported. However hypothermia should not cause much problem in management once recognised.

Termination of pregnancy

The value of termination of pregnancy in eclampsia is undisputed. Opinions differ regarding the time of induction and use of caesarean section (Menon, 1961; Greenhill, 1965; Eastman, 1966); Lean et al (1968), advocate caesarean section at the end of 1 hour of starting the treatment. The remarkably low rate of recurrence (2.2%), the low maternal mortality (3.3%) and lowest perinatal mortality (11.1%) achieved by them justify their high incidence of caesarean section (63%). In our series with a waiting period of 12 hours, incidence of caesarean section has been 6% and our recurrence rate, maternal and corrected perinatal mortality figures of 3.3% 3.3%, 16.6% respectively are well comparable to the figures of Lean et al, 1968. Perhaps in selected cases one could extend the waiting period to some extent to prevent caesarean section but not indefinitely, for then one would land up with the problem of intercurrent eclampsia and it's associated dangers. Moreover lower segment caesarean section in the present day obstetric management is quite safe.

We feel that diazepam by virtue of its hypnotic, muscle relaxant, anticonvulsant effect can be a suitable single drug replacement for lytic cocktail in the management of eclampsia. It is easier to understand and treat the side effects when one drug is being administered rather than 3 different drugs.

Conclusions

1. Prompt control of convulsions with termination of pregnancy at proper time by suitable method improves the foeto-maternal prognosis.
2. Diazepam does arrest eclamptic convulsions as effectively as it can control other convulsive disorders.
3. Serious complications like respiratory and cardiac failure are not encountered and this is because diazepam does not depress the vital centers like other sedatives.
4. A single drug therapy instead of the combination largactil, phenargan and pethidine is easier to administer.
5. Because of the lesser grades of unconsciousness the inherent complications of coma are lessened and nursing care becomes much easier.

Acknowledgement

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References