Diazepam Intoxication in Neonates

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Pregnancy induced hypertension (PIH) is a common obstetrical complication. Diazepam in frequent intravenous bolus doses is the commonest sedative used in managing severe PIH. We report four neonates presenting with features of cerebral depression as a result of diazepam intoxication.

Case Report

A girl weighing 3.0 kg was born to a 20-year-old primigravida. Ten days prior to the expected date of delivery the mother showed clinical features of severe PIH. There was no evidence of fetal distress. The mother was managed by intravenous bolus doses of diazepam (95 mg over next 24 h), oral nifedipine, and labetalol. Twently four hours later, she delivered the neonate. At delivery the neonate was severely asphyxiated, with an Apgar score of 3/10 and 7/10 at one and five minutes, respectively. Following initial resuscitation the neonate showed clinical features of cerebral depression with poor cry, hypotonia, and areflexia. The treatment included intravenous fluids, aminophylline (10 mg stat followed by 6 mg 8 hourly for the next forty eight h), oxygen by hood and antibiotics.

Over the next 48 h the neonate continued to show signs of cerebral depression including altered sensorium, generalized hypotonia, and poor neonatal reflexes requiring close monitoring and intravenous fluids. By 72 h there was marked improvement in sensorium and return of normal tone. However, reflexes including sucking reflex were still ill-sustained. Hence, the neonate was started on gavage feeds. Subsequently, the neonate showed increased improvement and by the seventh day she was able to feed on breast. The infant did not show any neurological sequelae during follow up.

Over the next few months we saw 3 similar cases. The second case was a female neonate born to a second gravida mother with severe PIH. The mother received injection diazepam (40 mg over 18 h), nifedipine, and labetalol. The neonate had moderate birth asphyxia followed by cerebral depression. Two other neonates were born to mothers with mild PIH who had received oral diazepam (10 mg per day for 10 to 12 days). These neonates did not have birth asphyxia. However, both showed mild cerebral depression at 1 h after birth. The progress and management of these four neonates is shown in the *Table.*

Discussion

The adage that one person's meat may be another's poison can be especially trying when the two individuals are connected by placental circulation(1), is true in the management of PIH. Diazepam is extensively used as an anxiolytic drug during labor and for control of seizures in eclampsia. It readily crosses placenta. Studies with C-14

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TABLE –*Clinical Profile of Neonates with Diazepam Toxicity.*

Feature	Case 1	Case 2	Case 3	Case 4
Diazepam dosage (in mother)	95 mg IV	40 mg IV	100 mg (12 d/oral)	120 mg (10 d/oral)
Birth asphyxia	Severe	Severe	No	No
Features (1 hr postnatal)	Coma Hypotonia Areflexia Hypothermia	Obtunded Hypotonia Areflexia	Lethargy Hyporeflexia	Lethargy Hyporeflexia
Sarnath stage	III	III	I	I
Treatment	IV fluids deriphylline	IV fluids deriphylline	Gavage feeds	Gavage feeds
Progress (recovery in days)				
Sensorium	2	2	-	-
Tone	3	3	-	-
Reflexes	5	5	-	-
Acceptance of feeds	8	7	3	3
Sequelae	Nil	Nil	Nil	Nil

labelled diazepam have shown a rapid transfer with higher concentration in cord blood one hour after administration(2). The metabolism by the fetal liver is minimal, and high concentrations of diazepam and its active metabolites have been demonstrated for upto 12 days after birth in neonates whose mothers had received moderate (10-15 mg) to large (90 mg) doses of diazepam(3). In addition the developing brain is more sensitive than that of the adult to centrally acting drugs, probably because a deficiency of myelin allows greater drug penetration(4). Significant depression was seen in all the four neonates in this report. In addition the first two neonates had severe asphyxia requiring active resuscitation. The clinical spectrum in diazepam intoxication ranges from 'floppy baby syndrome' characterized by hypotonia, lethargy, respiratory depression, hypothermia and poor reflexes to just lethargy and poor feeding.

Many drugs have been evaluated for their efficacy in reversing the effects of diazepam, though with little success. Benzodiazepines act by potentiating the effects of gamma-amino butyric acid at all levels of neuroaxis(5). The specific antidote has to relate to this electrophysiologic mechanism. Such a drug is flumazenil, currently not available in India(6). The other drugs used are physostigmine, naloxone, and aminophylline. Aminophylline with non-specific action on cortical arousal, has been used with satisfactory results in diazepam

intoxication of neonates(7). However, our experience shows that it does not have any therapeutic usefulness. This is quiet understandable because pharmacologically aminophylline has no specific action against diazepam.

With a view to avoid the adverse effects of diazepam on the fetus and neonate, it is suggested that alternative drugs like flurazepam and lorazepam be used. These benzodiazepines have shorter half life, are not converted to active metabolites and at the same time give adequate sedation in eclampsia.

REFERENCES

1. Editorial. Iatrogenic diseases of newborn. Lancet 1961, 2: 753.
2. Indanpaan Heikkila JE, Jouppila PI, Poulakka JO, Vorne MS. Placement transfer and fetal metabolism of diazepam in early human pregnancy. Am J Obstet Gynec 1971, 109: 1011-1013.
3. Cree JE, Meyer J, Hailey DM. Diazepam in labor: its metabolism and effect on clinical condition and thermogenesis in newborn. Br Med J 1973, 4: 251-253.
4. Seth SD, Seth V, Beotra A. Pharmacological principles of Pediatric therapeutics–Part I. World Pediatr Child Care 1985, 1: 51-65.
5. Trevor AJ, Way WC. Sedatives and hypnotics. *In:* Basic and Clinical Pharmacology, 3rd edn. Eds Bertram G, Katzung, California, Appleton and Lange, 1987, pp 241-253.
6. Reeves JG, Peter SA. Hypnotics. *In:* Anesthesia, 3rd edn. Ed Miller RD. New York, Churchill Livingstone, 1990, pp 251-254.
7. Kumar A, Man Mohan, Anand NK. Aminophylline in neonatal diazepam intoxication. Indian Pediatr 1987, 24: 602-604.

Oral Steroids in the Treatment of Periorbital Hemangioma

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Hemangiomas are common tumors of infancy(1). Nearly 90% of them resolve without complications or significant cosmetic deformity(2). Eventhough most of the hemangiomas resolve spontaneously, those occurring over special locations like eyelids, subglottic area, need immediate treatment. Various treatment modalities are available for treatment of hemangiomas. The commonly used methods include, surgical resection when small, intralesional steriod injection and in recent years, pulsed dye laser in early superficial lesions(1). Non-availability of pulsed dye laser, morbid fear of surgery, anesthesia and injections near vital organs like the eye make these modalities of treatment unsuitable for most of our patients.

Systemic steroids are suggested for treatment of visual or respiratory obstruction caused by a rapidly enlargng hemangioma or to treat the complications of Kasabach-Merrit Syndrome(3). We report a one-month-old infant with large

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