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Case Series

Neonatology Section

Adverse Drug Reaction following Injection of Amikacin Sulphate in a Cluster of Preterm Newborns

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ABSTRACT

Although, single case reports regarding adverse effects of Inj. Amikacin sulphate in newborns have been published, simultaneous affection of multiple babies is rare. In this report we present cluster of newborns admitted in a neonatal intensive care setup presenting with Adverse Drug Reaction (ADR) to Inj. Amikacin sulphate. It can cause life threatening adverse effects and neonates are particularly vulnerable to ADR.

Keywords: Adverse drug reaction, Amikacin sulphate, Neuromuscular blockade, Preterm newborns

ADR with Inj. Amikacin sulphate has been reported in many cases but is rarely serious. In our literature search, we did not found any report of a cluster of cases with ADR to Injection Amikacin sulphate. Hence we are reporting this cluster of newborns who simultaneously developing ADR in NICU setup.

CASE REPORT

A cluster of preterm low birth weight newborns admitted in a Neonatal Intensive Care Unit (NICU) in a Medical College setup developed severe ADR after administration of the night dose of antibiotics.

The details of the event are as follows: 13 babies were on Injection Amikacin sulphate (15 mg/kg/day in 2 divided doses) in the NICU of our Tertiary Care Hospital as per protocol for neonatal sepsis [1]. The nurse in charge of administration of antibiotic injection in NICU prepared the doses as per the NICU protocol for the night dose [2,3]. During the administration of the drugs when the sixth baby was injected, the mother of the baby who had received the first dose of Injection Amikacin sulphate complained that her baby has become lethargic and had bluish discolouration of the whole body. As the NICU staff attended the first baby, the other four babies also started developing similar symptomes. Immediate assessment and management of all 5 babies was initiated. The sixth baby was already on ventilator support and developed only transient cyanosis hence we could not exactly define whether the baby had suffered an ADR. There after Inj. Amikacin sulphate was stopped for all remaining babies in NICU and batches of other the antibiotics being administrated simultaneously viz. Inj. Piperacillin/tazobactum (300 mg/kg/day in 3 divided doses) and Inj. Cefotaxime (100 mg/kg/day in 2 divided doses) were substituted. Later on, after change of antibiotics, no further adverse events were reported.

There were two pairs of preterm twins among the 5 babies. i.e., first pair was case 1 and 2. Second pair was case 4 and 5. Case 3 was preterm baby from single pregnancy.

Details of the cases has been described in [Table/Fig-1]. Common antibiotic being administered to all babies was Inj. Amikacin sulphate. All 5 babies were vitally stable and none of them had any history of apnoeic spells before the adverse event.

Twin pair 1 and case 3 developed cyanosis, hypotonia, bradycardia while twin pair 2 also developed pallor and mottling along with the aforesaid symptoms.

ADR was reported to pharmacovigilance program and antibiotic samples were sent to FDA for analysis which was reported as normal.

DISCUSSION

An ADR has been defined by the World Health Organization (WHO) as 'any noxious or unintended drug response at doses commonly used for prophylaxis, diagnosis or treatment of a disease or condition [4].

Neonatal clinical pharmacology aims to assess inter and intra individual variability among different subjects and by that to predict and estimate adverse effects at the level of the population or preferably, the individual infant [5,6].

In recent studies related to iatrogenesis in NICUs, 33% cases were preventable, of which about 25% were related to medical errors [7,8].

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
	All babies were male, intramural and with normal vaginal delivery				
Weight and Gestational age	1900 grams (32-34 weeks)	1400 grams (32-34 weeks)	1700 grams (32-34 weeks)	1700 grams (32-34 weeks)	1800 grams (32-34 weeks)
Diagnosis at the time of admission	PTVD at 32-34 week of GA with AGA with mild RD with asymptomatic hypocalcaemia with early onset of sepsis.		PTVD at 36-38 week of GA with SGA with LBW with treated mild RD with early onset of sepsis.	PTVD at 36-38 week of GA with SGA with LBW with suspected early onset of sepsis.	
Age (in days) at time of ADR	6		2	2	
Treatment on going before ADR	IV fluid (ISOLYTE- P) Inj. Piperacillin/tazobactum (5 days) Inj. Amikacin (6 days) Inj. Calcium gluconate RT feeding		IV fluid (10% dextrose) Inj. Cefotaxime (2 day) Inj. Amikacin (2 days) Inj. Calcium gluconate	IV fluid (10% dextrose) Inj. Cefotaxime (2 day) Inj. Amikacin (2 days) Inj. Calcium gluconate	
	Antibiotic used therapeutically for respiratory distress with early onset of sepsis.			Antibiotic initiated for suspected early onset of sepsis.	
Treatment of ADR	All babies were incubated; Ambu and O2 support given; Inj. Normal saline and Inj. Adrenaline given. All 5 cases required ventilator support due to persistent apnoea. Case 1 was put on ventilator support in our hospital while other four cases were shifted to other hospitals for ventilator support.				
	Amikacin was replaced by Netilmycin and Piperacillin/tazobactum was replaced by Meropenem. After change of antibiotics no further adverse event occurred.				
Course after ADR and Outcome	Ventilator weaned off next day and after that oxygen support given for 2 days, RT feeding restarted on day of life 9 and Discharged on 15th day of life.	Shifted back to our hospital on oxygen support on next day, oxygen support omitted on day of life 9 and RT feeding restarted. Discharged on 15th day of life.	Shifted back to our hospital after 3 days, oxygen support given for a day, RT feeding started same day and Discharged on 9th day of life.	Ventilator support given for 4 days in other hospital but could not survive.	

[Table/Fig-1]: Details of cluster of cases.
Abbreviation: PTVD: Preterm vaginal delivery , GA: Gestational age , AGA: Appropriate for gestational age, RD: Respiratory distress.

Adverse Drug Reaction, Assessment Criteria	Yes	No	Not Applicable	Score in Case Group
Was the timing of AE consistent with an ADR to the suspected drug?	6	-7	0	6
Is the AE a well-documented ADR to the suspected drug?	0	-6	0	0
Are there published reports on this AE that are related to the suspected drug in newborns?	4	-4	0	4
Was the AE likely to be a change (exacerbation, recurrence, complication or new manifestation) in a Pre-existing clinical condition?	-3	7	0	7
Are there any alternative etiological candidates other than the pre-existing condition (e.g. Concomitant drugs) that are a common cause of the AE?	-3	2	0	2
Was an alternative etiological candidate confirmed by any objective evidence?	-3	3	0	3
Did the AE improve after the suspected drug was discontinued?	4	-1	0	4
Was the AE less severe when the dose was reduced?	4	-2	0	0
Did the AE improve after a specific antagonist was administered?	3	-1	0	0
Did the AE significantly diminish or disappear while the patient was still taking the suspected drug?	-2	1	0	0
Did the AE reappear/worsen when the suspected drug was reintroduced?	9	-1	0	0
Was the suspected drug detected in blood or other fluids in concentrations known to be toxic?	4	-2	0	0
Is there unequivocal evidence that the amount of the suspected drug received was an overdose for this patient?	4	-4	0	-4
*Total score				22

[Table/Fig-2]: Adverse drug reaction algorithm for neonate in NICU[12] and relative score in case group.
*If total score ≥14 → definite; 7 ≤total score ≤13 → probable; 3 ≤total score ≤6 → possible; total score ≤2 → unlikely
Abbreviations are as follows: ADR, adverse drug reaction; AE, adverse event

Differentiation of 'true' ADRs from confounding reactions associated with organ dysfunction, immaturity and underlying diseases remains difficult. New ADR assessment score [Table/Fig-2] is more valid and reliable as compared to the Naranjo algorithm, ADR assessment score is based on 13 simple yet informative questions [8,9].

Ototoxicity, nephrotoxicity and neuromuscular blockade are known adverse reactions of Amikacin sulphate [10]. Calcium transfer from mother to fetus takes place mainly in last trimester, so preterm babies are prone to hypocalcemia and they have high chances of neuromuscular blockade [11].

In this case report, primary evaluation suggested adverse reaction to Inj. Amikacin sulphate based on the ADR assessment score which was 22 for each of the babies thus falling in "Definite ADR" category. All the babies had the same score since they had similar background of predisposition and epidemiology.

This ADR is likely to be due to neuromuscular blockade action of Amikacin sulphate. Once this drug was withdrawn and antibiotic was changed, no further adverse event occurred which further supports the possibility of ADR.

Since, all the babies in the cluster of babies reported by us were preterm and the literature clearly mentions prematurity to be a risk factor for ADR, in this event prematurity was no doubt a significant predisposing factor. However, since the event involves a single episode which was in the backdrop of no unusual or new methodology of drug preparation or administration and the process of preparation of actual injection is not monitored, it is not possible to establish the actual reason which may have precipitated this crisis.

CONCLUSION

Medication error can lead to ADR and errors can occur at multiple levels, starting from the manufacturing of the drug to the delivery to the patient. It can either be a human or technical error. Neonates, particularly preterm and low birth weight are especially prone to such ADR. This was an example of high vulnerability of newborn babies to ADR of antibiotics, doctors and nurses should follow strict protocol to avoid such events in future.

The need for a mechanism of monitoring of medication in newborns, particularly in the critical care setup cannot be over emphasised and should be appropriately implemented with multiple levels of scrutiny right from prescription to post drug administration surveillance.

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