

ADVERSE DRUG REACTIONS IN PEDIATRICS WITH A STUDY OF IN-HOSPITAL INTENSIVE SURVEILLANCE

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ABSTRACT

A two-part prospective study of adverse drug reactions (ADRs) in Indian children was carried out at a teaching general hospital. Using an in-hospital intensive surveillance scheme (IISS) for the detection of ADRs, indoor patients of one of the two units in the pediatric ward were monitored daily for 6 months, with the other unit serving as a control group. A total of 347 patients were monitored, 2781 daily orders written and 24,474 doses of 96 different drugs given. Six patients suffered from ADRs (1.73%), and 1 reaction proved fatal (0.29%), while the control group reported only 1 ADR in the same time period. The frequency of ADRs ($p < 0.001$) and their resultant mortality in Indian children was less than that in a western prototype study. Though IISS showed a marked increase in ADR reporting, it was too cumbersome for routine use in our country.

In the second part of the study, 40 cases of ADRs seen over 2 years were analyzed. Antimicrobials, especially sulphonamides, accounted for a high percentage of cases mostly as skin rashes and fairly severe reactions were common. Patients on anti-tuberculous and anti-convulsant drugs required prolonged supervision for late onset reactions.

Key words: Adverse drug reactions, Intensive in-hospital surveillance, Post marketing surveillance, Fatal drug reactions.

Adverse drug reactions (ADRs) are a frequent though neglected problem in clinical pediatrics. Such cases very rarely get reported and very few systematic studies on this aspect pertaining to children have been carried out, particularly in our country. Most surveillance schemes for ADRs are hampered by gross under reporting(1) and thus it is difficult to gauge the true incidence of adverse reactions.

In-hospital intensive surveillance (IISS) as a method for detecting ADRs was first tried in the Boston Collaborative Drug Programme (BCDP)(2). This method is the most comprehensive surveillance scheme available, with almost no under reporting(3). There are no reports in the literature on studies in Indian children using this method.

Our study which comprised a pilot study of in-hospital intensive surveillance and an analysis of drug reaction cases, was, therefore, undertaken to gauge the incidence of ADRs and analyse drug reactions in Indian children, and to assess the usefulness of the in-hospital intensive surveillance scheme for ADR detection in our country.

Material and Methods

In-hospital intensive surveillance for ADRs as per the BCDP protocol was carried out over 6 months from 1st August 1989 to 31 January, 1990 in a Pediatric Unit of Nair Hospital, Bombay.

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Patients present in the ward were assessed every day by the same doctor for the presence of any suspected ADR. A record was also kept of what drug every patient received that day and the number of doses given. An algorithm was used to determine the causal relationship between the drug and the event (Fig.) (4). Cases considered as almost definite and highly probable were

considered as adverse drug reactions. The details of the reaction were noted and the patient monitored.

The other unit in the same department, with an equal number of beds, attending physicians, and emergency days, served as a comparison group, voluntarily reporting any suspected ADR to the worker, who then evaluated the case as above. Thus, in IISS,

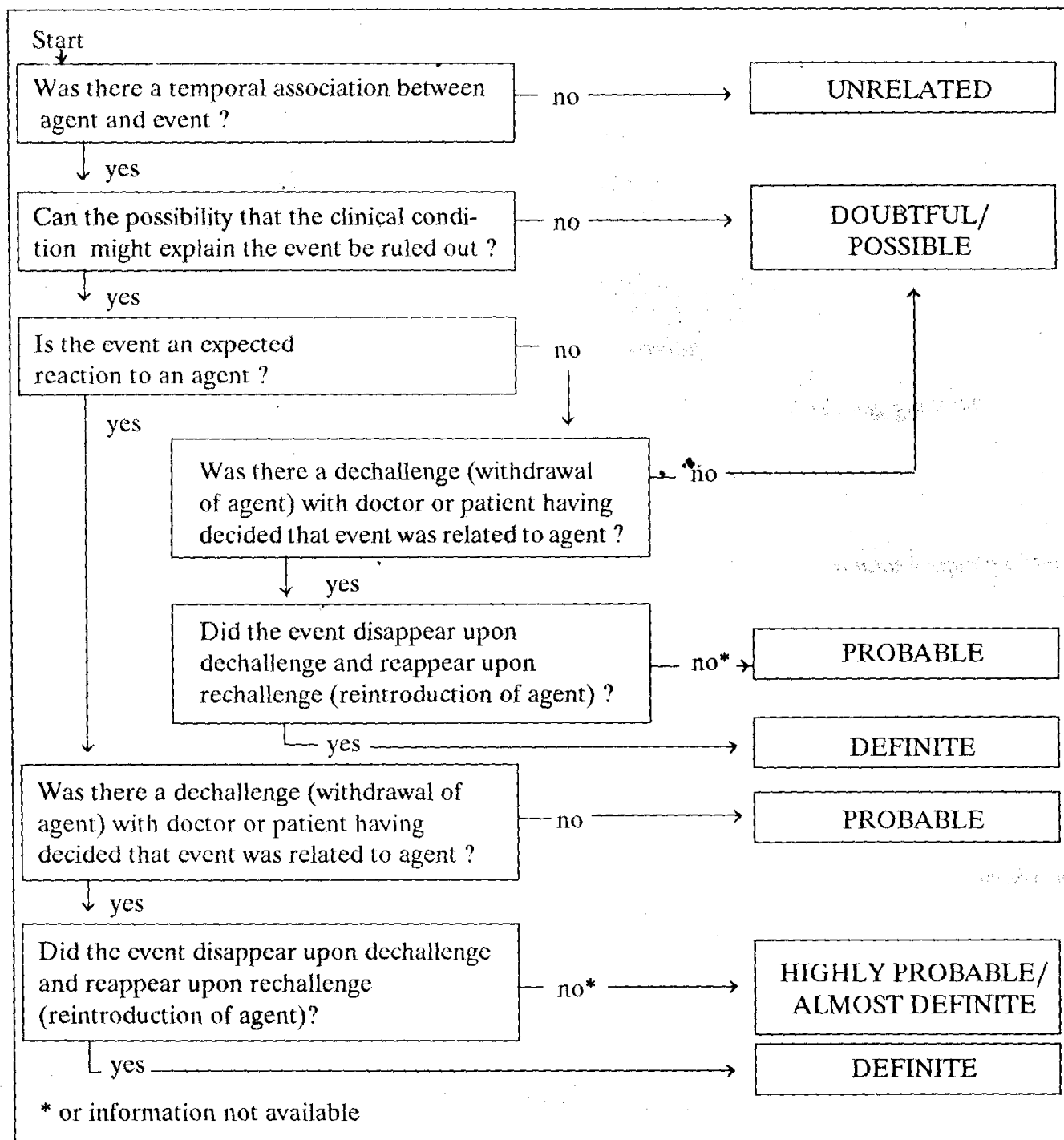


Fig. Algorithm for causal relationship in ADRs.

the worker was specifically looking for ADRs, whereas in voluntary reporting the doctor might have missed an ADR, or failed to report it even if it was recognized.

In the other part of the study 40 cases of ADRs seen in children in both in and out-patient departments were documented for two years from March 1988 to May 1990. All suspected ADRs were evaluated as per the same algorithm. Cases were excluded from the study if (i) they fell in the 'unlikely' category (most cases fell into the 'highly probable' category as we did not do rechallenge for ethical consideration); (ii) the name of the drug could not be ascertained; (iii) the dose or the number of doses administered was not known; (iv) when multiple drugs were given, of which more than one was equally likely to have caused the reaction except in cases of antituberculous therapy (AKT); and (v) the patient did not follow up for assessing the response.

Laboratory investigations were performed only on those patients with overt clinical manifestations, who had a biochemically or hematologically measurable abnormality, e.g., hepatitis or aplastic anemia. Drug levels in blood were not performed due to unreliable results and inadequate facilities.

Results

In the intensive in-hospital surveillance scheme, 347 patients were monitored over 6 months, 96 different drugs used, 2781 daily orders written and a grand total of 24,474 doses of various drugs given to the patients.

As depicted in *Table I*, 6 patients suffered from ADRs, 2 due to antituberculous therapy, and one each due to sulphonamides, phenytoin, aspirin and amoxycillin. The overall incidence of ADRs was 1.73% for patients and 0.202% for orders. One drug related death was seen, due to Stevens-Johnson syndrome following sulphonamide administration. Prolongation of hospital stay because of the ADR was seen in 0.28% of patients.

During the same time period, the other unit, serving as a control group, voluntarily reported only 1 case of an ADR out of 363 patients in six months. Utilizing the monthly records of age and illness distribution maintained by our department, a comparison of the age distribution and illness pattern during the same time period showed both groups to be comparable. Standard treatment protocols for most of the in-patients were the same in both groups.

TABLE I—Surveillance Scheme Results

Drug	Number of patients given the drug	Number of reactions	Type of reactions	% of patients	% of doses
AKT	72	2	Hepatitis	2.77	0.326
Sulphonamides	44	1	Stevens-Johnson Syndrome	2.27	0.259
Phenytoin	15	1	Skin rash	6.66	1.09
Aspirin	11	1	Salicylism	9.09	0.497
Amoxycillin	6	1	Skin rash	16.67	2.5

During the presurveillance period March 1988 to August 1989 (17 months), only six cases of in-patient ADRs were brought to the notice of the worker, as compared to six in just 6 months during the surveillance period (0.3/ month vs 1.0/ month).

The frequency of ADRs with the individual drugs is given in *Table I*.

In the two-year analysis of cases, drug reactions were seen in all age groups including newborns. A slight male preponderance (1.4 : 1) was evident. The different drugs that were involved in ADRs are seen in *Table II*, and the reactions encountered are given in *Table III*. Hospitalization for the treatment of the drug reaction and/or prolongation of hospital stay, indicative of severe reactions, were seen in 40% of the cases. Though the majority of the cases (77%) occurred within the first 10 days of starting therapy, a significant number (22.5%) occurred later. AKT and anti-convulsants were responsible for all the cases

in this group. All the drug reactions due to these two groups also took longer to resolve while the others resolved within 4 days (*Table IV*).

Discussion

The detection of adverse drug reactions is hampered by the inherent drawbacks of most post-marketing surveillance schemes(5). Most of these schemes, *e.g.*, spontaneous reporting(6), voluntary reporting(7), medical record linkage(3), and mandatory reporting(1), suffer from gross under-reporting of ADRs, which reduce their efficacy.

In-hospital intensive surveillance, first developed by the Boston Collaborative Drug Program (BCDP)(1-4), is the most comprehensive of all the monitoring systems, and has virtually no under-reporting. It, therefore, is the best system for calculating incidence rates of ADRs, and evaluating possible causal associations between certain adverse events and drugs.

TABLE II—Drugs Involved in Reactions (in 2-Year Study Period)

Drug	No. of cases with ADR	%	Drug	No. of cases with ADR	%
Antimicrobials	24	60	CNS Dgurs	7	17.5
Sulphonamides	10	25	Phenytoin	5	
Ampicillin	8	20	Phenobarbitone	1	
Amoxycillin	2		Haloperidol	1	
Penicillin	2				
Erythromycin	1				
Chloramphenicol	1				
AKT	3	7.5	Miscellaneous	6	15
			Aspirin	2	
			Digoxin	1	
			Aminophylline	1	
			Iron	1	
			Amphotericin	1	

TABLE III—Reactions Encountered in 2-Year Study Period

Reactions	n
Skin rashes	22
Stevens-Johnson syndrome	2
CNS manifestations	7
Acute gastroenteritis	7
Hepatitis	3
Angioneurotic edema	2
Aplastic anemia	1
	44

TABLE IV—Late Onset and Prolonged Reactions in 2-Year Study Period

Drug group	n	Time of onset > 10 days	Duration of reaction > 4 days
AKT	3	3	3
Anticonvulsant medication	7	6	7
Others	30	Nil	Nil

Comparing our results with those of the BCDP pediatric study(3), we found that our incidence of drug reactions, both per patient (1.73/100 versus 25/100) and per order (0.202/100 versus 5.2/100), was lower than that reported by the BCDP, and statistically highly significant ($p < 0.001$).

On analyzing the illness pattern in the BCDP study, it was observed that a large percentage of their patients comprised leukemics (5%), and that the largest number of ADRs occurred in this group (3.3% of all ADRs were bone marrow depression). The BCDP authors themselves opined that this

represented a difficulty in data interpretation for them, and may have led to their high ADR frequency. Leukemia comprised less than 1% of our study group which may account for our lower ADR incidence. Otherwise, the age and illness pattern was comparable in both groups, with infections, convulsive disorders, and asthma being the commonest illnesses.

Similarly, when comparing the fatal drug reaction rates, we found the mortality to be less in Indian children (0.29%) than in the BCDP study (0.55%), though this was not statistically significant.

AKT induced overt hepatitis is seen in approximately 1% of patients(9), though this varies with the number and types of drugs used. INH alone was shown to cause hepatitis in 0-1% in one study, while inclusion of other drugs increased its frequency up to 4-5%(10). Our figure of 2.7% ADRs with INH, rifampicin, pyrazinamide and streptomycin in two to four drug combinations is thus within the reported range.

A BCDP follow-up study on cotrimoxazole reported that out of 2622 children receiving this drug, 2.5% developed adverse reactions, mainly in the form of skin rashes and gastrointestinal complaints(11), which is nearly identical to our figure of 2.27%. Phenytoin has been reported to cause skin reactions ranging from urticaria to Stevens-Johnson syndrome, in 5-10% of patients(12), which corroborates with our value of 6.6%. Other BCDP follow-up studies on amoxycillin and aspirin have reported ADR rates of 3.3 and 4.9%, respectively(13,14). Our figures of 16.6 and 9.09% cannot be compared as the number of patients who received these drugs in our study was very small.

Though our study reported a male preponderance of 1.4 : 1, this has not been found by other workers. We postulate this male preponderance to be due to the

preference shown to male children in our country at all levels. Siedl(15) found antimicrobials alone to be responsible for 41% of reactions in his series, while our study implicated this group in 60% of the cases. Ogilvie(16) and Caranasos(17) also found certain groups of drugs, such as antimicrobials, digoxin, and diuretics, to be involved in ADRs more frequently than other drugs. Skin rashes were the most frequent manifestation seen by us, and also reported by Hoddinott(18), though Miller(19) found gastrointestinal complaints to be more common.

Davies(5) has stated that almost all reactions occur within the first 11 days of starting a drug, but our experience showed that as many as 25% of the reactions occurred even afterwards. All of these reactions were due to AKT or anti-convulsants, and took longer to resolve than other reactions. Long term supervision of such patients is indicated to prevent late onset toxicity.

In-hospital intensive surveillance has been reported to be the best way of detecting the maximum adverse drug reactions, as also evidenced in our study where a 6-fold increase in reporting was recorded as compared to voluntary reporting. Though the types of ADRs seen in our IISS study such as Stevens-Johnson syndrome and hepatitis are not likely to be missed by clinicians, they frequently go unreported in voluntary reporting systems, thereby reducing the value of such voluntary schemes. Despite this, we feel that IISS is too expensive and time consuming for routine use in our country. This original BCDP used nurse monitors for detection, which would not be feasible in our country, as they would require specialized training. Using a doctor as a monitor as done by us, is also impractical, as the doctor would then not be able to devote time to his other work, unless specially

appointed for the same. Other system of surveillance will have to be found, which are less expensive, but give a higher yield of drug reactions.

REFERENCES

1. Gross FH, Inman WHW. Drug Monitoring *In: Proceedings of an International Workshop*. Eds Gross FH, Inman WHW. New York, Academic Press, 1979, pp 27-32.
2. Sloane D, Jick H. Drug surveillance using nurse monitors. *Lancet* 1966, 2: 901-903.
3. Lawson DH, Shapiro S, Sloane D, Jick H. Boston Collaborative Drug Program—Drug Surveillance: Problems and Challenges. *Pediatr Clin Amer* 1972, 19: 117-129.
4. Stephens MDB. The Detection of New Adverse Drug Reactions, New York, Stockton Press, 1985, pp 102-104, 236.
5. Davies DM. Textbook of Adverse Drug Reactions, 2nd edn. Ed Davies DM. Oxford, Oxford Medical Publications, 1981, pp 3-8.
6. Finney DJ. Design logic of a monitor of drug use. *J Chr Dis* 1965, 18: 77.
7. Karth F, Lasagna E. Adverse drug reactions—A matter of opinion. *Clin Pharm Ther* 1976, 19: 489-492.
8. Finney DJ. Systematic signalling of adverse reactions to drugs. *Methods of Information in Medicine* 1974, 13: 1-10.
9. Girlin DJ. Reviews on the adverse effects of anti-tuberculous agents. *Drugs* 1982, 23: 56-61.
10. Girling DJ. The hepatotoxic effects of anti-tuberculous regimens. *Tubercle* 1978, 59: 13-15.
11. Jick SS. Adverse effects of cotrimoxazole in children. *Lancet* 1984, 2: 631.
12. Reynold JEF, Martindale. The Extra Pharmacopea, 29th edn. London, The Pharmaceutical Press 1989, pp 101-102, 401-405.

13. Biqby M. Ampicillin and Amoxycillin-toxicity. *J Am Med Assoc* 1986, 256: 3358-3359.
 14. Miller RR, Jick H. Adverse reactions with aspirin. *Am J Med Sci* 1977, 274: 271.
 15. Seidl LG, Thornton GF, Cluff LE. Epidemiological studies of adverse drug reactions. *Am J Pub Hlth* 1965, 55: 1170.
 16. Ogilvie RI, Ruedy J. Adverse drug reactions during hospitalization. *Can Med Assoc J* 1967, 97: 1450-1452.
 17. Caranasos A, Feinstein AF. Biostatistical problems of pharmaceutical surveillance. *Clin Pharmacol Ther* 1974, 16: 110-123.
 18. Hoddinott BC. Drug reactions and errors in administration in a medical ward. *Can Med Assoc J* 1967, 97: 1001.
 19. Miller RR. Drug surveillance using epidemiological methods. *Am J Hosp Pharmacy* 1973, 30: 584-592.
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