Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 22s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Pharmacovigilance Study on Safety Assessment of Nicorandil

Vishwas Pathak[*1], Rajesh Sharma[2]

[*1,2]School of Pharmacy, Devi Ahilya Vishwavidyalaya Indore Indore, Madhya Pradesh-452001, (India)

***Corresponding Author:**

Vishwas Pathak

Email ID: vishwas.pathak@gmail.com

Cite this paper as: Vishwas Pathak, Rajesh Sharma, (2025) Pharmacovigilance Study on Safety Assessment of Nicorandil. *Journal of Neonatal Surgery*, 14 (22s), 1105-1111.

ABSTRACT

Background: The chronic use of the antihypertensive drugs make patients more vulnerable to experience adverse effects that are either known to occur (expected adverse drug reactions) or are not known to occur (unexpected adverse drug reaction, previously unknown adverse reaction). Pharmacovigilance is the science and activites related to the continuous assessment of benefit risk profile of the drug to understand the safety profile of the drug for continuous use.

Aim and Objective: Pharmacovigilance study was conducted to study the safety profile of Nicorandil in patients of hypertension.

Study Design: Non-interventional, observational, cohort study.

Materials and Methods: The study was conducted using active drug surveillance methodology of pharmacovigilance. The valid individual case safety reports were identified from the Pub Med database using international nonproprietary name <Nicorandil>. The coding of event terms was done using medical dictionary for drug regulatory activity. WHO-UMC causality assessment scale was used for performing cause and effect analysis.

Results and Discussion: A total of 18 valid case reports with 19 adverse drug reactions were identified (males=09; females=08; missing demographic detail = 01). Maximum patients (n=12) were in the age group of 70-80+ years and least number of patients were in the age group of 40-50 years. Comparison of reported ADR(s) was done with EMEA Summary of Product Characteristics of Nicorandil. The ADR 'Cyanosis' was not reported in the EMEA SmPC , however the same was reported in our study. Occular side effects were identified as signals from the study. Conclusion: All reported ADR(s) are expected except the ADR of 'Cyanosis'. The expected ADRs are well known to occur with formulations containing Nicorandil.

Keywords: *Nicorandil, Pharmacovigilance, adverse drug reaction, cohort study, hypertension*

1. INTRODUCTION

During past two decades a large volume of newly introduced drugs have been witnessed for the treatment of various ailments and to meet out the unmet medical need of the patients. With this surge in the drug discovery the safety aspects of the newly discovered drugs have also become a major concern as there is always a very minimal information on the safety profile of the drug during clinical development phase. The reasons for this mainly include clinical study short duration, subject selection criteria basis which a large number of population category, for example, children, pregnant woman, nursing mothers, elderly, renally and hepatically compromised patients, and other diseased condition patients get excluded from the study. Consequently the information generated during the clinical study on safety aspects is not enough to assess the benefit-risk profile of the drug for the continuous use of the drug in 'real world clinical practice .

Pertinently, in Indian population, among various non communicable diseases cardiovascular diseases exert a substantial burden. A large number of Pharmacoepidemiological studies have been conducted on prevalence of cardiovascular diseases. These studies have reported hypertension to be one of the major cardiovascular risk factor causing significant mortality and other comorbidities in Indian population.[(1)].

Currently a large number of medicinal products are available to control hypertension by reducing blood pressure. Also recently, trials have been conducted for the assessment of the efficacy of the antihypertensive agents for cardiovascular risk reduction. Such clinical studies have also proposed goals for treatment [(2-4)] and management of hypertension in patients with other comorbid factors and requiring other concomitantly administered drugs. Because of clinical trial limitations, the results

from these pharmacoepidemiological studies and other clinical studies are not sufficient enough to define the benefit-risk profile of the drug in 'real world' clinical situation for the continuous use of the drug. This necessitates the assessment of the adverse drug reaction profile to be ascertained at periodic time intervals for the understanding of the positive benefit risk profile of the drug.

As per WHO, Pharmacovigilance is the science and activities that deals with the collection, assessment, detection and understanding of the adverse drug reactions reported after the use of drug. Since the treatment and management of essential hypertension mandates the chronic use of antihypertensive therapy for long term use, Accordingly predisposition to adverse drug events due to the usage of antihypertensive drug during chronic use is highly probable.

Since, Nicorandil ,is widely prescribed as a one of the line of treatment for the management of hypertension by the physicians in India, so, the aim of this present prospective, observational, cohort study was to determine the incidence and assessment of causality of ADRs of antihypertensive drugs occurring in patients of essential hypertension.

2. METHODS

Study design : Non-interventional observational cohort study conducted using 'active surveillance' methodology of pharmacovigilance.

The individual case safety reports (ICSR(s)) were identified from the PubMed database. The reports reported after the administration of the active constituent 'Nicorandil' were included for the purpose of inclusion as PubMed case reports. Validation of individual case safety reports was done using valid criteria for ICSR(s). An individual case safety report was considered as valid case report if it contained following four information:

I. Identifiable Patient:

A patient was categorized as an identifiable patient if there was information on any of the following

- Age/Date of Birth
- Gender
- Weight/ Height
- Ethnicity

II. Suspected Drug: The study drug Nicorandil was considered as suspected drug. For the purpose of the study the suspected drug with "Active Constituent" name / International Non Proprietary Name was searched in the PubMed database.

III. Suspected Event : The information on adverse drug event after the administration of Nicorandil as suspect drug was considered in the study.

IV. Reporter Information: The details of the reporting author(s) was recorded.

In the present study since the case reports were identified from the literature database 'PubMed' accordingly as per international guidelines on "Good Pharmacovigilance Practices" [5] the implied causal association ship was considered between the drug and the event and thus because of the implied causal association ship all events were considered as adverse drug reactions. Since the adverse drug information were identified from the published literature , hence all reported reactions were considered as " Medical Confirmed" cases.

The adverse event information was entered in the data base (Excel sheet) using the dictionary that has a hierarchial structure arranged by system-organ class. The terminology used by the reporter in the individual case safety report was grouped under 'lower level terms' (LLT) which are in turn grouped under 'preferred term' (PT), 'high level term' (HLT), 'high level group term' (HLGT) and to the respective system-organ class (SOC) . For a single published literature if more than one case was identified, it was given a separate case ID. Any other means/format of reporting ADRs were also accepted, if it contained at least the following information: identifiable patient, identifiable reporter, suspected drug name, adverse drug reaction term / description.

A comparison for the occurrence of suspected ADRs expressed as <Reported>; <Not Reported> was done with the EMEA SPC of "Nicorandil 10mg" film-coated tablets. In the EMEA SPC of "Nicorandil 10mg" film-coated tablets, the listing of undesirable effects is based on data from controlled clinical trials and from post marketing surveillance.

The analysis was conducted for seriousness of the adverse drug reaction. An adverse drug reaction was categorized to be serious if the outcome resulted into either death; hospitalization, prolongation of existing hospitalization, permanent incapacity/disability, congenital anomaly , or birth defect, important medical event (IME).

3. STATISTICAL ANALYSIS

Descriptive statistics was applied to calculate the number of reports, to classify the reports gender and age wise, to provide number of adverse drug reactions. Coding of events reported as suspected ADRs was done using Medical Dictionary for Regulatory Activities (MedDRA) terminology[6]. All drug-related adverse events were evaluated according to the "WHO Probability Assessment Scale" [7] (Table 1).

TABLE 1: WHO PROBABILITY ASSESSMENT (CAUSALITY ASSESSMENT) SCALE FOR ADVERSE DRUG REACTIONS

Category Description

1. Certain: A clinical event, including laboratory test abnormality, that occurs in a plausible time in relation to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure, if necessary.

2. Probable : A clinical event, including a laboratory test abnormality with a reasonable time relation to administration of drug, unlikely to be attributed to concurrent disease or other drug or chemical and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

3. Possible : A clinical event, including laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drug or chemicals.

4. Unlikely : A clinical event including a laboratory test abnormality, which makes a causal relation improbable, and in which other drugs, chemical or underlying diseases provide plausible explanations.

5. Conditional / unclassified: A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment, or the additional data are being examined.

6. Inaccessible/unclassifiable : A report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified.

As per WHO causality assessment criteria, ADR were classified as Certain, Probable, Possible, Unlikely,

4. RESULTS

The results for screening yielded a total of 1042 publications including results from clinical trials, meta analysis, randomized clinical trial, review and systemic review. Of these 1042 publication a total of 58 individual case reports were screened. These 55 case report publications were further evaluated and identified for 'valid case safety report'. From a total of 55 case reports, a total of 18 individual case safety reports were identified. A total of 17 case reports were analyzed as valid case safety reports as the details of age and sex was missing for one case report.

The adverse drug reaction reports identified from different countries is shown in **Table 2.** Among the cohort, the ethnicity data was available for one ethnic type, that is White British man. Other demographic characteristics related to comorbid conditions and concomitantly administered drug are present in **Table 3.**

Table 2: Country wise classification

Country	Number of Reports
France	2
India	1
Japan	3
Republic of Korea	1
Sri Lanka	1
Taiwan	1
United Kingdom	9
Total = 18	

Table 3: Demographic Characteristics

Reported Comorbid Conditions

Diabetic Nephropathy
Dizziness
Shortness of Breath
Hypothyroidism
Angina
Venous Thromboembolic disease
Weight Loss
Change in bowl habbit

Prescribed/Administered Concomitant drugs

Ferrous citrate
Furosemide
Spironolactone
Tolvaptan
Bisoprolol
Warfarin
Esomeprazole
Digestive enzyme complex
Ambroxol

The age and sex distribution of the patients is shown in Table 4. There were 09 males and 08 females and the data for age and sex was missing for 01 patient. Among males there were seven case reports that reported elderly age group and one case from Japan reported age 41 years whereas in case of females all females comprised of elderly age group. The mean age (± s.d.) was 73± 13 years. Maximum number of patients (12) were in the age group of 70-80^{+} years.

.The least number of patients were in the age group of 40-50 years. The drug exposure duration with nicorandil varied from few weeks of initiation of therapy to a maximum of 14 years. The dosage strength included 5 mg, 10mg, 20mg and 30mg as oral formulation. No pregnancy was reported. The smoking status was also not reported in the case reports. The medical history of the patients included,history of history of unexplained significant weight loss and change in bowel habit

End Stage Renal Disease,Diabetic Nephropathy, Atrial fibrillation, Angina,Chronic Obstructive Pulmonary Disease, Ischaemic Heart Disease, Hypertension, Hypothyroidism, High serum creatinine, Abdominal pain and diarrhea.

Table 4: Age and Sex Distribution

AGE (Year)	**Males**	**Females**	**Total**
30 – 40	NIL	NIL	NIL
40 – 50	01	NIL	01
50 – 60	NIL	02	02
60 – 70	01	01	02
70 – 80+	07	05	12
Unknown	Unknown	Unknown	01
Total	**9**	**8**	**18**

Suspected ADRs:

A total of 19 suspected adverse drug reactions (ADRs) were reported (Table 5).

Table 5: Suspected ADR

Adverse Events	Preferred Term	No. of ADRs
EXPECTED		
Colonic Ulceration	Intestinal Ulcer	1
Corneal Ulcer	Ulcerative keratitis	1
Corneal Perforation	Corneal perforation	1
Skin ulcer	Skin ulcer	2
Headache	Headache	1
Nerve Palsy	Third nerve paralysis	1
Ulcer	Ulcer	2
UN EXPECTED		
Hyperkalemia	Hyperkalemia	2
Lack of Efficacy	Drug Ineffective	1
Penile ulceration	Penile ulceration	2
Parastomal ulceration	Ulcer	1
Colitis	Colitis	1
Cyanosis	Cyanosis	1
Pseudomelanosis	Gastrointestinal mucosal pigmentation	1
Vulval ulcer	Vulval ulcer	1
Total		**19**

Per analysis conducted for seriousness category of the adverse drug reaction(s) all eighteen individual case reports were categorized as serious adverse drug reaction reports.

The seriousness criteria as important medical event (IME) was reported in seventeen individual case safety reports. 'Death' as an outcome was reported as a seriousness criterion in one patient. The outcome was reported as 'recovered' in 13 individual case reports whereas the information on outcome was not available for four case safety reports.

Death as an outcome was reported in 41-year-old man who was admitted to hospital with history of chest pain and dyspnea. High dose of propofol was given along with mechanical ventilation. On hospital admission day 4, there was a blockage in the atrioventricular region noted, which subsequently induced cardiopulmonary arrest. Per reporter nitroglycerine and nicorandil was ineffective.

5. DISCUSSION

The other comorbid conditions such as diabetes, kidney ailments and other coronary artery diseases associated with the patients suffering from hypertension make them more vulnerable for the drug related adverse effects. The aim of the present study was the identification and assessment of the adverse drug reactions occurring due to the use of Nicorandil in hypertensive patients. Although our study reported the co morbid conditions and the use of other concomitant medications in similar pattern to that found in literature [6-7], the other risk factors like gender, age, BMI, waist circumference, alcohol consumption, disease history, blood pressure rate, cigarette packs used, and sedentary lifestyle were also considered.[8]

In the present study the resolution in the adverse drug reaction(s) were seen in a total of eleven patients. In one of the patient

the adverse drug reaction of penile ulceration was resolved on stopping the treatment with nicorandil [9]. In another case report the adverse effect of corneal ulceration got resolved with in six weeks after withdrawal of nicorandil [10]. The reports of ocular side effects induced by Nicorandil were reported as rare and probably underestimated. The adverse effect of corneal perforation, glans hernia, hyperkalemia, fistula of rectovaginal area, colitis, ulceration, intractable headache, right ptosis, bluish tinge was also reported which got resolved after cessation of the drug nicorandil [11-17]. Although in the past mucocutaneous ulcerations have been considered as attributable to nicorandil, however the report of corneal damage was considered as major corneal damage due to nicorandil. In the present study the reported case of methemoglobinemia appears to be case of special interest and can be monitored in future to evaluate the benefit risk profile.

The WHO causality assessment scale showed that all reported adverse drug reactions were 'probably' related to the study drug Nicorandil.

6. CONCLUSION

Pharmacovigilance mainly deals with the study of safety profile of the drug and to further analyse any previously unreported adverse drug reactions. Since the patients undergoing treatment of hypertension makes the usage of plethora of other drugs as well, the adverse drug profile of nicorandil was studied to identify the potential adverse adverse drug reactions and to further study any previously unknown adverse drug reaction. The outcome of the present study highlights the nature and severity of adverse drug reactions with Nicorandil. The reported adverse drug reaction(s) in the present study were comparable with the existing safety profile of the Nicorandil as seen in EMEA summary of product characteristics. The report of corneal ulceration and corneal perforation were treated as signal and needs to be monitored in future. The reports of ulceration in our study were similar to reports identified by the Pharmacovigilance programme of India (a WHO collaborating center for Pharmacovigilance in Public Health Programmes and Regulatory Services) in year 2017 and 2022 respectively, as these were recommended to be added in the product information by the Marketing Authorization Holders.

REFERENCES

[1] Longkumer, I., Yadav, S., Rajkumari, S. et al. Trends in hypertension prevalence, awareness, treatment, and control: an 8-year follow-up study from rural North India. Sci Rep 13, 9910 (2023). https://doi.org/10.1038/s41598-023-37082-4.

[2] Whelton PK, Carey RM, Aronow WS, et al. ACC / AHA / AAPA / ABC / ACPM / AGS / APhA / ASH / ASPC / NMA / PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. Hypertension 2018;71: e13-115.doi:10.1161/ HYP.0000000000000065.

[3] Williams B, Mancia G, Spiering W, et al, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-104. doi:10.1093/eurheartj/ehy339.

[4] Wright JTJr, Williamson JD, Whelton PK, et al, SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood Pressure Control. N Engl J Med 2015;373:2103-16. doi:10.1056/ NEJMoa1511939..

[5] Guideline on good pharmacovigilance practices (GVP)Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 28 July 2017. EMA/873138/2011 Rev 2.

[6] Desai N, Unni G, Agarwala R, Salagre S, Godbole S, Dengra A, Abhyankar MV, Revankar S. Risk Factors and Comorbidities in Young Indian Patients with Hypertension: REAL YOUNG (Hypertension) Study. Integr Blood Press Control. 2021 Feb 26;14:31-41. doi: 10.2147/IBPC.S272548. PMID: 33664586; PMCID: PMC7924245.

[7] Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021–3104.

[8] World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva, Switzerland: World Health Organization; 2013. Available from: https://www.who.int/nmh/events/ncd_action_plan/en/Accessed. Accessed March 14, 2024.

[9] Yap D, Aboumarzouk O, Bates C. Nicorandil-induced penile ulceration: a case report. J Med Case Rep. 2016 Jul 16;10:194. doi: 10.1186/s13256-016-0987-3. PMID: 27423333; PMCID: PMC4947313.

[10] Trechot F, Batta B, Petitpain N, Bazard MC, Angioi K, Trechot P. A case of nicorandil-induced unilateral corneal ulceration. Int Wound J. 2014 Jun;11(3):238-9. doi: 10.1111/iwj.12081. Epub 2013 May 7. PMID: 23651162; PMCID: PMC7950522.

[11] Campolmi N, Guy C, Cinotti E, Forest F, Gain P, Philippe-Zech C, Gauthier AS, Thuret G. Corneal perforation: another side effect of nicorandil. Cutan Ocul Toxicol. 2014 Jun;33(2):96-8. doi: 10.3109/15569527.2013.812105. Epub 2013 Jul 11. PMID: 23845070.

[12] O'Neill P, Brown R. Penile Ulceration Secondary to Nicorandil Use. Urol Case Rep. 2016 Dec 11;10:57-59. doi: 10.1016/j.eucr.2016.11.008. PMID: 27981036; PMCID: PMC5153433.

[13] Chowdhry V, Mohanty BB. Intractable hyperkalemia due to nicorandil induced potassium channel syndrome. Ann Card Anaesth. 2015 Jan-Mar;18(1):101-3. doi: 10.4103/0971-9784.148331. PMID: 25566721; PMCID: PMC4900302.

[14] McCormack P, Skelly R. A demonstration of peristomal ulceration in the setting of nicorandil therapy. BMJ Case Rep. 2014 Nov 12;2014:bcr2014206599. doi: 10.1136/bcr-2014-206599. PMID: 25391826; PMCID: PMC4244338.

[15] Samra K, Manikam L, Pathmakanthan S. When treatment can be worse than the disease: nicorandil-induced colitis. BMJ Case Rep. 2015 May 24;2015:bcr2015209799. doi: 10.1136/bcr-2015-209799. PMID: 26009604; PMCID: PMC4458621.

[16] Sharma A, Orpin S, Goulding JM, Kaur MR. Two cases of nicorandil-induced ulceration mimicking skin malignancy. Br J Dermatol. 2014 Sep;171(3):662-3. doi: 10.1111/bjd.12978. Epub 2014 Aug 22. Erratum in: Br J Dermatol. 2015 Jan;172(1):308. Goulding, J [corrected to Goulding, J M R]; Kaur, M [corrected to Kaur, M R]. PMID: 24836355.

[17] Jeong SH, Kim H. Acute intractable headache and oculomotor nerve palsy associated with nicorandil: A case report. Am J Emerg Med. 2017 Dec;35(12):1988.e3-1988.e5. doi: 10.1016/j.ajem.2017.10.006. Epub 2017 Oct 5. PMID: 29033341.

[18] File No: P.17019/01/2018/-PvPI, Dated January 31,2023, Indian Pharmacopoeia Commission (Ministry of Health and Family Welfare, Government of India, Sector 23-Raj Nagar)