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Consideration of ethnic factors during drug approval process

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ABSTRACT

Purpose

To determine feasibility of drug registration for the selected drugs at USFDA based on the ICH E5 guideline.

Methods

Methodology involves two steps, they are 1. Determination of ethnic sensitivity of the selected drugs based on factors such as pharmacokinetics (PK), pharmacodynamic (PD), therapeutic range, and metabolism etc., given in appendix D of ICH E5 guidelines. 2. Determination of the need for the bridging studies after determining ethnic sensitivity of the selected drugs based on the ICH E5 guidelines.

Results

After the extensive analysis of the selected drugs, drugs like nicorandil, may be ethnically insensitive based on ICH E5 guideline.

Drugs like, nicorandil, may be approved by USFDA without need of bridging studies because they are ethnically insensitive and medical practice across the ICH countries is mostly similar. The efficacy and safety of these drugs is demonstrated by the fact that these drugs are on the market for at least 25 years and prescribed in the millions of the patients.

Conclusion

Nicorandil may be ethnically insensitive among the selected drugs based on the ICH E5 guideline. Drugs like nicorandil may be approved by USFDA (United States Food and Drug Administration) without need of bridging studies.

INTRODUCTION

There is need for study of ethnic factors when a drug has to get approval in the foreign locations where the clinical trials of drug have not been conducted to avoid duplication of the clinical studies, which are already done with lot of expenses because, for the development of a single drug it take years and 802 million dollars. [1] In this context, The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued ICH E5 guidance in February 1998 regarding the ethnic factors in the acceptability of foreign clinical data. The ICH E5 guideline provide a general frame work for evaluating the potential impact of ethnic factors on the acceptability of foreign clinical data, with the underlying objective of minimizing duplication of clinical data and it also describes the requirement of bridging study for extrapolation of foreign clinical data to a new region.

NEED FOR THE STUDY

All countries acknowledge the desirability of utilizing foreign clinical data that meet the regulatory standards and clinical trial practices acceptable to the region considering the application for registration.

However, concern that ethnic differences may affect the medication's safety, efficacy, dosage and dose regimen in the new region has limited the willingness to rely on foreign clinical data. Historically, this has been one of the reasons, therefore, the regulatory authority in the new region has often requested that all, or much of, the foreign clinical data in support of registration be duplicated in the new region. Although ethnic differences among populations may cause differences in a medicine's safety, efficacy, dosage or dose regimen, many medicines have comparable characteristics and effects across regions. Requirements for extensive duplication of clinical evaluation for every compound can delay the availability of new therapies and unnecessarily waste drug development resources.

The purpose of ICH E5 guidance is to facilitate the registration of medicines among ICH regions by recommending a framework for evaluating the impact of ethnic factors upon a medicine's effect, i.e., its efficacy and safety at a particular dosage and dose regimen. It provides guidance with respect to regulatory and development strategies that will permit adequate evaluation of the influence of ethnic factors while minimizing duplication of clinical studies, cost, time and supplying medicines expeditiously to needy patients for their benefit. [2]

To realise full potential of ICH E5 guideline goals, there is need to identify and register more drugs which are approved for their efficacy and safety in one country and prescribed in the millions of the patients for the decades and not approved in the another country based on the ICH E5 guideline by appropriate institutions like World Health Organization (WHO), Non-Governmental Organizations (NGOs'), pharma companies etc., to realize the goals of ICH E5 guideline.

In this context drugs approved in the Japan for the decades and whose efficacy and safety is proved by the fact that they are prescribed in the millions of the patients are identified and there feasibility of registrations at United States Food and Drug Administration (USFDA) is studied to realise the goals of ICH E5 guideline.

RATIONALE FOR THE SELECTED DRUGS

After the extensive analysis of literature, drugs like Nicorandil, because this drug were not available for the patients in USA even though the efficacy and safety of the this drug is well proved and demonstrated by the fact that this drug is on the market in the ICH group of countries like European union and Japan for at least 15 years and prescribed for the millions of the patients. [3]

USA being an important player in ICH group of countries may take full advantage of this fact by providing these drugs to its needy patient population at earliest by evaluating these drugs based on the ICH E5.

Approval of These drugs with or without bridging studies based on the ICH E5 guideline helps in the realization of the goals of ICH E5 guideline i.e., minimizing duplication of clinical studies, cost, time and supplying medicines expeditiously to needy patients for their benefit at the right time.

In this context, drugs whose efficacy and safety is well established and approved in the Japan for

the decades are identified and there feasibility for registrations at USFDA is studied to realise the goals of ICH E5 guideline.

AIM OF THE STUDY

To determine feasibility of drug registration for the selected drugs at USFDA based on the ICH E5 guideline.

Objectives of the study

1. To determine ethnic sensitivity of the selected drugs based on factors given in appendix D of ICH E5 guidelines.
2. To determine the need for the bridging studies after determining ethnic sensitivity of the selected drugs.

METHODOLOGY

Methology involves following parameters. They are as follows

Regulatory consideration

As per ICH E5, the pharmaceutical industry should first submit the clinical data package. The clinical data package would be assessed by the regional regulatory authority regarding the nature and quality of the data, irrespective of its geographic origin. A clinical data package would be defined as a "complete" clinical data package for submission and potential approval if it meets all of the regional regulatory requirements. Foreign clinical data component of the complete data package can be acceptable depending upon whether it can be extrapolated to the population of the new region. ICH states that clinical trials should be designed and conducted according to regulatory standards in the new region, be adequate and well-controlled, utilize endpoints that are considered appropriate for assessment of treatment and clinical disorders should be evaluated using medical and diagnostic definitions that are acceptable to the new region. If clinical data does not fit into the above criteria, it might not be accepted.

Regional regulatory authority might ask for additional clinical trials if the foreign clinical data do not meet the regional regulatory requirements.

Ethnic consideration

A medicine's sensitivity to ethnic factors can be judged by pharmacokinetic, pharmacodynamic, or other characteristics which suggest the potential for clinically significant or minimal impact by intrinsic and/or extrinsic ethnic factors on safety, efficacy and dose response.

The critical properties of a medicine for assessment of sensitivity to ethnic factors have been enumerated in appendix D of the ICH E5 guideline. The critical properties of a medicine that make it less likely to be sensitive to ethnic factors include linear pharmacokinetics (PK), flat pharmacodynamic (PD) curve, wide therapeutic range, minimal metabolism, high bioavailability, low potential for protein binding, little potential for interactions, nonsystemic mode of action, and little potential for inappropriate use.

The critical properties of a medicine that make it more likely to be sensitive to ethnic factors include nonlinear pharmacokinetics (PK), steep pharmacodynamic (PD) curve, narrow therapeutic range, high metabolism, genetic polymorphism, administration as a prodrug with the potential for ethnically variable enzymatic conversion, high inter-subject variability, low bioavailability, high likelihood of use in a setting of multiple co--medications and high potential for inappropriate use. [2]

Analysis of the selected drugs for the requirement of bridging studies

ICH E5 define bridging study as a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region.

Generally, for medicines characterized as insensitive to ethnic factors, the type of bridging study needed (if needed) will depend upon experience with the drug class and upon the likelihood that extrinsic ethnic factors (including design and conduct of clinical trials) could affect the medicine's safety, efficacy, and dose-response.

A bridging study may not be needed in following two conditions if (a) Medicine is ethnically insensitive and extrinsic factors such as medical practice and conduct of trials are similar in each region and (b) Medicine is ethnically sensitive

but the two regions are ethnically similar and there is sufficient experience with pharmacologically related compounds in the two regions.

Bridging study with pharmacologic endpoints may be needed if region is ethnically dissimilar, drug is ethnically sensitive, but extrinsic factors are similar, a controlled PD study in new region using a pharmacologic endpoint or established surrogate endpoint could bridge foreign data.

A controlled clinical trial in the new region may be necessary when there are doubts about choice of dose, there is little or no experience with acceptance of controlled clinical trials conducted in the foreign region, medical practice is different between regions (e.g., concomitant medication, control arm), drug class is not familiar to new region or pharmacodynamic data suggest interregional differences in response.

Even if foreign clinical data demonstrate safety and efficacy, there may still be a safety concern in the new region regarding need to accurately determine rates of common adverse events in new region and need to detect serious adverse events in the new region. [2]

All the above factors are summarized in the following table. [2, 15]

Table 1: Requirement for the Bridging Studies

Medicine	Ethnicity of region	Medical Practice	Drug Class	Clinical Experience	Bridging Studies
Ethnically Insensitive	-	Similar	-	-	No
Ethnically Sensitive	Similar	-	-	Sufficient	No
Ethnically Sensitive	Dissimilar	Similar	Familiar	-	PD
Doubts about choice of dose	-	Different	Unfamiliar	Insufficient	CCT
Safety concern in the new region	Need to accurately determine rates of common adverse events in new region Need to detect serious adverse events in the new region				safety study

PD: Pharmacodynamics; CCT: Controlled clinical trials

The selected drugs will be determined whether there are ethnically sensitive or not based on parameters discussed above, then the requirement of the bridging study will be determined based on the following table.

SUMMARY OF THE METHODOLOGY

Selection of the drug

⬇

Analysis of the drug based on factors given in appendix D of ICH E5 guidelines to determine ethnic sensitivity

⬇

After analysis, drugs are compared with the table for the requirement of the bridging studies.

RESULTS

After the extensive literature search, few drugs were selected. Analysis of one drug, Nicorandil, is presented here. Each of these drugs were evaluated on the criteria laid down in ICH E5 guideline for its sensitivity to ethnic factors and requirement of bridging study for extrapolation of foreign clinical trial data. Nicorandil is analysed and results are presented as below.

Nicorandil

Nicorandil belongs to the class of compounds known as potassium channel activators which are

characterized by their arterial vasodilator properties. In addition, nicorandil has venodilating properties which are attributable to a nitrate group in its chemical structure. Therefore, by combining these two vasodilator mechanisms, nicorandil represents a novel type of compound for use in the treatment of angina pectoris. Furthermore, increasing experimental evidence suggests that potassium channel activation may also exert a direct cytoprotective effect by augmenting normal physiological processes which protect the heart against ischaemic events. [16]

Bioavailability

After oral administration, nicorandil is absorbed rapidly and maximum plasma concentrations are reached after about 30-60 minutes. [17, 21] The absolute bioavailability of nicorandil is 75±23%, indicating that no significant first pass effect exists. [37, 38] Although food has been shown to delay the absorption of nicorandil (16%), it does not affect the extent of absorption. Thus nicorandil tablets can be taken with meals. [17, 21]

Protein Binding

Nicorandil is not extensively bound to human plasma proteins (free fraction estimated to be about 75%). [17, 21]

Linearity of Pharmacokinetics

The plasma concentrations (the area under the curve) show linear proportionality to the dose (5 mg to 40 mg). The drug disposition parameters (distribution volume, mean residence time, total body clearance and apparent elimination half-life) remain unchanged within the therapeutic dose range. [16, 17, 18]

Metabolism and Prodrug Character

Nicorandil is metabolized extensively and the major route of elimination is through kidney [32, 36], Less than 2% of the dose is excreted through the biliary route. As a consequence the parent drug is excreted poorly in urine (very low renal clearance), whereas 2-nicotinamidoethanol, a pharmacologically inactive denitrated metabolite, is the major nicorandil related compound excreted in urine. [17, 21, 23]

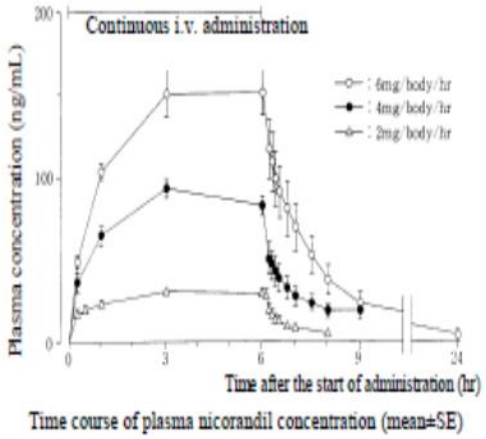

Fig 2: Concentration-time curves of nicorandil [19, 20]

Interactions & Use in a Setting of Multiple Co-medications

No pharmacological or pharmacokinetic interactions have been observed in humans or animals with beta-blockers, digoxin, rifampicin, cimetidine, acenocoumarol, a calcium channel blocker or a combination of digoxin and furosemide. Nevertheless, there is the possibility that nicorandil may potentiate the hypotensive effects of other vasodilators, tricyclic antidepressants or alcohol.

As the hypotensive effects of nitrates or nitric oxide donors are potentiated by phosphodiesterase

5 inhibitors, the concomitant use of nicorandil and phosphodiesterase 5 inhibitors is contraindicated.

Gastrointestinal perforations in concomitant use of nicorandil and corticosteroids have been reported. Caution is advised when concomitant use is considered. [17, 20, 21, 24]. There are interactions with nicorandil which can be taken care by proper presentation in prescribing information.

Pharmacodynamics

In reported clinical study, 12 mild to moderate hypertensive patients were taken to investigate acute antihypertensive efficacy of three different doses of nicorandil. All doses of nicorandil similarly and significantly ($P < 0.01$) reduced supine blood pressure, with a peak after 4-6 hour (10 mg: -21/-8 mm of Hg; 20 mg: -20/-9 mm of Hg; 30 mg: -29/-17 mm of Hg), The three different doses of nicorandil caused similar acute blood pressure reductions without change in the heart rate, or in the urine volume and urinary sodium [25] indicating that pharmacodynamic curve is flat.

Efficacy studies

The efficacy of nicorandil is well established. Clinical usefulness of this product was shown in two separate series of double-blind controlled clinical studies conducted in patients with various types of angina pectoris. The response rates of the product in various types of angina pectoris in open clinical studies (21 reports of Phase II & III studies) are summarized below.

Table 9: Response rates of the Nicorandil in various types of angina pectoris in open clinical studies

Diagnosis	Efficacy rate (Good response or better)
Total	72.2% (369/511)
Effort angina	69.8% (185/265)
Effort and rest angina	69.1% (96/139)
Rest angina	94.3% (50/53)
Variant angina	73.0% (27/37)
Post-infarction angina	64.7% (11/17)
(including) Unstable angina	82.4% (14/17)

Nicorandil is an effective and potent antianginal agent at a dose of 10-40 mg, which in monotherapy controls 69-80% of patients with stable chronic angina. [20]

Relative efficacy

Clinical studies employing exercise tolerance test as major end point show that nicorandil at doses 10 to 20 mg twice daily is as efficacious as other anti-anginal agents (including diltiazem, nifedipine, isosorbide mononitrate, isosorbide dinitrate, propranolol, metoprolol and atenolol) in treating patients with chronic stable angina. Long-term uncontrolled studies show that nicorandil maintains its efficacy with no evidence of tolerance developing up to 2 years after commencement of therapy. [17, 21, 26]

Nicorandil medication affords similar improvement as propranolol in patients with angina pectoris. [42]

Comparative trials have shown that the efficacy of nicorandil compares with that of drugs from the main classes of antianginal drugs- beta-blockers (atenolol, propranolol) and a calcium channel blocker (diltiazem). Patients treated for as long as 3 months or 1 year have shown sustained efficacy to the drug. The long duration of action allows effective treatment with a well-tolerated twice a day regimen. [28]

The efficacy of nicorandil in preventing coronary artery spasm in patients with vasospastic angina was compared to nifedipine in provocation test using methylergometrine. Nicorandil was shown to be at least as effective as nifedipine. [17, 28]

A systematic review study suggests therapy with nicorandil is as effective as standard therapy and that nicorandil can also be used as a first-line agent in patients with stable angina. [29]

Nicorandil exerts its pharmacodynamic actions even in the state of nitrate tolerance induced by Isosorbide Mono-Nitrate (ISMN). The antianginal and anti-ischemic effects of nicorandil are long lasting, allowing a twice a day dose regimen for the treatment of Coronary Artery Disease (CAD). Nicorandil is effective in the long-term treatment of

angina pectoris in the dose range of 10-40 mg twice a day. It is well tolerated, and only a few dose adjustments were necessary during long-term therapy. [30]

Safety

In the European clinical development programme, the total incidence of adverse events among nicorandil recipients was reported to be similar to that in patients who received comparator drugs. Mild to moderate headache was the most frequently reported adverse event, occurring in 36% of patients with angina pectoris treated with oral nicorandil. The incidence of headache was highest during initial treatment with the drug but generally resolved within a few days. Headache was the most frequent reason for treatment withdrawal in the European clinical development programme, accounting for 5% of all withdrawals in nicorandil recipients, and was less frequent with a lower dosage (5 mg twice daily) than a higher dosage (10 mg twice daily).

A later prescription-event monitoring study involving 13, 260 patients also reported that headache was the most frequent adverse event reported during nicorandil treatment (9.4 events per 1000 patient-months during the treatment period). [26]

Safety has been assessed in a total of 1680 subjects who were treated with nicorandil, with 458 patient years of exposure to treatment. Adverse events usually occurred early in the course of treatment. After 30 days of treatment, fewer than 10% of patients reported adverse events. [31]

A Prescription Event Monitoring (PEM) study of nicorandil was undertaken to assess the drug's overall safety in everyday clinical practice. The study was based on a cohort of 13,260 patients and 86,760 patient-months of nicorandil treatment. This PEM study reported information on the 'real-world' use of nicorandil and shows generally that the drug is safe when used in the recommended dosage. [32]

No clinically relevant modifications in the pharmacokinetics have been seen in the elderly, liver disease and chronic renal failure. [33, 34]

In comparative trials with anti-anginal agents, such as propranolol, diltiazem, nifedipine, Isosorbide Di-Nitrate (ISDN) and isosorbide 5 mononitrate, the overall incidence of adverse events was not significantly different between nicorandil and the reference drug. Side-effect distribution was comparable between nicorandil (32%) and diltiazem (30%).

Nicorandil can be safely combined with other anti-anginal drugs. Furthermore, due to its favourable pharmacokinetics, nicorandil is less likely to have interactions when combined with another therapeutic agent. Nearly one-third of the patients enrolled in the nicorandil clinical programme were 65 years old or older. Overall, the incidence of the most frequent adverse events in the elderly was reported to be similar.

There is no evidence that nicorandil induces proarrhythmia, exacerbation of myocardial ischaemia or abrupt withdrawal syndrome. With the progressive titration scheme, no symptomatic decrease in blood pressure was reported when nicorandil was administered in the range of 10–80 mg/day. Heart rate was not significantly affected in the same dose range. Long term treatment with nicorandil did not induce oedema or weight gain. Nicorandil did not adversely affect the lipid profile or the glucose level. [31] Other than headache, the most frequently reported adverse events were dizziness, nausea and malaise.

There have been case reports of mouth ulcers developing during nicorandil treatment, but there is at present no clear evidence of a causal relationship. [26] It is in the market for over 26 years. [20] Extensive clinical experience with nicorandil is considered to have demonstrated the therapeutic value of the compound and no new or unexpected safety concerns arose from the Nicorandil and it was therefore judged that the benefits of taking Nicorandil outweigh the risks.[34]

Therapeutic Dose Range (An Indicator of Safety & Tolerability)

Nicorandil has wide therapeutic range from 2.5 mg to 80 mg. [17, 19, 20, 21] There is no tolerance and cross tolerance to dosage as observed with nitrates. [17, 18, 19, 21] There is no experience of massive over dosage in humans and the LD_{50} in dogs is in the range 62.5 to 125 mg/kg and in rodents it is in the order of 1200 mg/kg. [24, 34]

Inappropriate Use

Nicorandil is not listed in the abused drug list of National institute on Drug Abuse therefore there is less scope for inappropriate use. [15]

SUMMARY OF THE NICORANDIL

Nicorandil belongs to the class of compounds known as potassium channel activators which are characterized by their arterial vasodilator properties. In addition, nicorandil has venodilating properties which are attributable to a nitrate group in its chemical structure. Therefore, by combining these two vasodilator mechanisms, nicorandil represents a novel type of compound for use in the treatment of angina pectoris.

The plasma concentrations show linear proportionality to the dose (5 mg to 40 mg) and it shows absolute bioavailability of nicorandil is 75±23% with no significant first pass effect. Nicorandil is not extensively bound to human plasma proteins (free fraction estimated to be about 75%) and it is metabolized extensively in liver and converted into pharmacologically inactive denitrated metabolites.

When patients were treated with nicorandil, the three different doses of nicorandil caused similar acute blood pressure reductions indicating that pharmacodynamic curve is flat. Clinical studies shows that nicorandil twice daily is as efficacious as other anti-anginal agents (including diltiazem, nifedipine, isosorbide mononitrate, isosorbide dinitrate, propranolol, metoprolol and atenolol) in treating patients with chronic stable angina. Long-term studies show that nicorandil maintains its efficacy with no evidence of tolerance.

Genetic polymorphism and inter subject variability with nicorandil is not reported and it has low potential for interactions. Moreover nicorandil is not listed in the abused drug list of National institute on Drug Abuse therefore there is less scope for inappropriate use.

Nicorandil has wide therapeutic range. Extensive clinical experience with nicorandil is considered to have demonstrated good safety profile value of the compound and no new or unexpected safety concerns arose from the Nicorandil .Therefore it can be concluded nicorandil is safe and well tolerated. Nicorandil may be ethnically insensitive as it satisfies most of the factors mentioned in appendix D of the ICH E5 for the ethnical insensitivity.

Table 10: Properties that make Nicorandil less sensitive to ethnic factors

S.NO	PARAMETERS	YES/NO
1	Linear pharmacokinetics	Yes
2	A flat pharmacodynamic	Yes
3	A wide therapeutic dose range	Yes
4	Minimal metabolism or metabolism distributed among multiple pathways	Yes
5	High bioavailability	Yes
6	Low potential for protein binding	Yes
7	Little potential for interactions	Yes
8	Non-systemic mode of action	NO
9	Little potential for inappropriate use	Yes

Table 11: Properties that make Nicorandil more sensitive to ethnic factors

S.NO	PARAMETERS	YES/NO
1	Non-linear PK	NO
2	A steep PD curve	NO
3	A narrow therapeutic dose range	NO
4	Highly metabolized	Yes
5	Genetic polymorphism	NO
6	Administration as a prodrug**,** with the potential for ethnically variable enzymatic conversion	NO
7	High inter-subject variability	NO
8	Low bioavailability	NO
9	High likelihood of use in a setting of multiple co-medications	Yes
10	High likelihood for inappropriate use	NO

DISCUSSION

After the extensive analysis of the selected drug, Nicorandil may be ethnically insensitive based on ICH E5 guideline. Drugs like Nicorandil may be approved by USFDA without need of bridging studies because they are ethnically insensitive and medical practice across the ICH countries is mostly similar. The efficacy and safety of these drugs is demonstrated by the fact that these drugs are on the market for at least 25 years and prescribed in the millions of the patients.

Approval of These drugs with or without bridging studies helps in the realization of the goals of ICH E5 guideline i.e., minimizing duplication of clinical studies, cost and supplying medicines expeditiously to patients for their benefit.

CONCLUSION

Nicorandil may be ethnically insensitive based on the ICH E5 guideline. Drugs like Nicorandil may be approved by USFDA (United States Food and Drug Administration) without need of bridging studies because they are ethnically insensitive and medical practice across the ICH countries is mostly similar.

FUTURE DIRECTIONS

Approval of nicorandil with or without bridging studies at various regulatory authorities in the world should be tried by appropriate institutions like WHO, NGOs', pharma companies etc., to realize the goals of ICH E5 guideline i.e., minimizing duplication of clinical studies, cost and supplying medicines expeditiously to needy patients for their benefit.

To realise full potential of ICH E5 guideline goals, there is need to identify and register more drugs which are approved in one country and not approved in the another country.

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