

Bioequivalence and Interchangeability of Narrow Therapeutic Range Drugs. Canadian Society for Pharmaceutical Sciences Discussion

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A Canadian Society for Pharmaceutical Sciences (CSPS) discussion group was held on August 23, 1997 in Edmonton, Alberta to discuss issues surrounding the bioequivalence of narrow therapeutic range (NTR) drugs. Participants in the discussion presented on topics related to sources of variability attributed to subject, target patient response and manufacturing as well as regulatory issues. This document represents a record of the discussion among the participants of the discussion group. It does not necessarily represent the policies or guidelines of the Canadian Society for Pharmaceutical Sciences (CSPS).

DISCUSSION OBJECTIVES

The objectives of the discussion were to:

- (1) identify sources of variability affecting bioequivalence determination for NTR drugs;
- (2) identify issues in the evaluation of bioequivalence and interchangeability of NTR drugs
- (3) review and comment on the draft directive '*Standards for comparative bioavailability studies involving drugs with a narrow therapeutic range - oral dosage forms*' recently circulated for comments by the Therapeutic Products Directorate, Health Canada, and to
- (4) prepare a record of the discussion to be used as a starting point for further discussion

The following questions were initially raised:

- are NTR drugs a distinct drug class or not?
- are the current bioequivalence standards sufficiently rigorous to ensure therapeutic (and safety) equivalence for NTR drugs?
- should more stringent standards be adopted?
- what are appropriate metrics (and acceptance ranges) for more stringent standards?

While it was hoped that the participants could reach a consensus on these issues and provide recommendations to this end, this was not the result. Rather, the group concluded that more work had to be done to determine whether the fact that the ratio between efficacy and toxicity is smaller for NTR drugs than for uncomplicated drugs justifies tighter controls for determination of bioequivalence. The underlying concern is that minor differences in serum or tissue

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concentrations may lead to unwanted toxicity. As a result, this report summarizes the discussion that took place on these issues as well as other topics raised at the meeting but does not include any recommendations at this time.

STATEMENT OF PROBLEM

As defined by the Therapeutic Products Directorate, Health Canada, a narrow therapeutic range (NTR) drug is a drug where the ratio of the lowest concentration at which clinical toxicity occurs, to the median concentration providing a therapeutic effect, is less than or equal to 2. An example of a NTR drug is theophylline [minimum toxic concentration (20 mcg/mL) : median effective concentration (10 mcg/mL) = 2]. Since small differences in the amount of NTR drug administered may result in more serious consequences than with 'uncomplicated' drugs, the required degree of assurance of the similarity of reference and subsequent-entry products is felt to be greater with NTR drugs than with 'uncomplicated' drugs (1).

Current bioequivalence standards for 'uncomplicated' drugs, as set forth by the Therapeutic Products Directorate, require that the 90% confidence interval (CI) of the relative mean log-transformed AUC of the test (T) to reference (R) formulation falls within 80-125% and the relative mean log-transformed C_{max} of the T to R formulation falls within 80-125%.(2).The 90% CI sets the consumer risk of incorrectly concluding a product is bioequivalent at 10%, commensurate with that of two one-tailed t-tests conducted at $\alpha=0.05$. The 80-125% range results from general agreement that for most 'uncomplicated' drugs, a -20 to +25% variation in plasma concentrations would not be considered clinically significant.

Modified bioequivalence standards for NTR drugs have been proposed by the Therapeutic Products Directorate since the prevailing opinion is that the required degree of assurance for the similarity of reference and subsequent-entry NTR drugs is greater than with 'uncomplicated' drugs. Greater assurance is achieved by proposing a 95% CI for AUC. This

reduces the consumer risk from 10% to 5% of incorrectly concluding a product is bioequivalent. In addition, a 95% CI is proposed to apply to C_{max} since for NTR drugs, toxicity is often related to concentration; hence, a limitation on variability is placed on the peak concentration resulting from the formulation. As well, a fed study is required in order to address food-formulation effects since seemingly small concentration changes can be clinically significant for NTR drugs. Overall, the modified standards are very similar to those suggested by the Expert Advisory Committee on Bioavailability in Report C circulated in 1992 (3).

International guidance on appropriate bioequivalence standards for NTR drugs is limited. Some authorities (European Commission, World Health Organization and Therapeutic Goods Administration (Australia)) have stated that for drugs with an especially NTR, the acceptance range for AUC may need to be tightened.¹ At present, the US Food and Drug Administration does not recognize a formal designation of NTR drugs and they do not believe that drugs fall into discrete groups that would allow one to consider NTR drugs as being clearly different from any other drugs for purposes of therapeutic substitution (4).

It would therefore seem that the major question that must be answered is - are there data in the literature that would support that substitution with generic products of NTR drugs actually leads to diminished efficacy or increased toxicity since the ratio of toxicity to efficacy for NTR drugs is small? If it is generally accepted that NTR drugs exhibit toxicity at doses close to those required for therapeutic effect, is it appropriate to apply the same bioequivalence criteria as used to assess 'uncomplicated drugs' regardless of the therapeutic range? The dilemma that arises is that even if a -20 to +25% variation between formulations of NTR drugs is found to be acceptable, there is potential for two different subsequent-entry NTR drug products to be interchanged at the pharmacy level. These products would have to have been shown to be bioequivalent with a given reference product but not with each other. If each subsequent entry product is allowed to vary from the reference by -20% to +25%, the amount they could potentially vary from each other may be of some concern. While this is not usually a

serious concern for 'uncomplicated' drugs, it is a concern for NTR drugs as they could be freely substituted at the pharmacy level.

SOURCES OF VARIABILITY

The presenters in the discussion group spoke on sources of variability which have potential to affect the determination of bioequivalence of NTR drugs. Sources of variability attributed to subject, target response in patients and manufacturing were discussed in detail by the group.

The way in which bioequivalence is currently determined was said to facilitate 'prescribability' rather than 'switchability' of generic products. Although calculation of 'average' bioequivalence may be an acceptable method for 'uncomplicated' drugs, NTR drugs may necessitate closer consideration of individual patient data (i.e. intrasubject variation and subject x formulation interaction) in order for the clinician and patient to be confident in the interchange of different formulations. The suggestion was made that application of 'individual bioequivalence' concepts to NTR drugs may be in order but this would warrant further discussion.

Sources of intrasubject variation in bioequivalence determination include genetic factors, physiologic factors such as GI motility, transit time and pH, age, co-morbid disease, concomitant drugs, body composition, hormonal balance, noncompliance, smoking and chronological factors. Bioavailability may also be altered by co-administration with food and the effect can be largely formulation dependant.

A point of concern that was discussed is that our current methodology for bioequivalence studies allows for manufacturers of subsequent-entry products to 'pre-select' the product used in the study from various batches (it was noted that they are supposed to be representative of production lots). The manufacturer can conduct dissolution tests on the batch prior to bioequivalence determination, thereby providing the opportunity to study only 'well formulated' batches. In addition, the brand name product used in bioequivalence trials is usually purchased from a local

pharmacy so can be 'pre-selected' to some extent as well. Concern was expressed that this practice could introduce bias into the bioequivalence determination.

The fact that 'real-life' bioequivalence is not being performed was also discussed as it applies to NTR drugs. Subjects used in bioequivalence studies are young, healthy males whose activity is restricted for the duration of the study. Perhaps, NTR drugs should be tested under clinical conditions and in the target population to accurately assess pharmacokinetic and pharmacodynamic differences between formulations. At present, all of the bioequivalence data for a given drug is based on a single point in time as there is no requirement for repeated bioequivalence testing to ensure that production batches of the subsequent-entry product remain bioequivalent with the innovator product i.e. "formulation creep". *In-vitro* dissolution testing for purposes of quality control should only be acceptable if it has been shown that there is a significant *in-vitro/in-vivo* correlation for the drug.

Variability in therapeutic outcome is a complex interplay of discrete factors such as clinician skill and experience and patient factors such as the indication for which the drug is being used, concomitant disease and drug variables. If a drug is being used 'off indication', outcome may be extremely variable as there have been no randomized, controlled, clinical trials to assess the therapeutic outcome. It is therefore, fundamentally important, to look at the nature of toxicity and whether toxicity is manifested as an extension of the therapeutic effect (e.g. warfarin) or if toxicity is apparent in other tissues and affects other body systems (e.g. lithium).

The importance of tight manufacturing specifications for NTR drugs was emphasized due to the drug formulation being recognized as a major source of variability. Current USP content uniformity specifications allow for the amount of active drug in a single tablet to vary by 85-115% (based on n=10 tablets). As a result, the permitted variation in drug content must be considered against two important factors. The first is the range of allowable dosage increments used in practice. For example, if dosage is routinely adjusted in $\pm 25\%$ increments, a $\pm 15\%$ permissible variation in tablet content is a concern

with NTR drugs. Similarly, for determination of bioequivalence between different formulations, if a -20 to +25% variance between two formulations of a drug is accepted, then a $\pm 15\%$ permissible variation in tablet content does not make good sense.

REGULATORY ISSUES

The group was presented with an overview of the regulatory issues pertaining to NTR drugs. A number of methods have been proposed thus far to ensure that the degree of assurance of the similarity of reference and subsequent-entry products for NTR drugs is greater than with 'uncomplicated' drugs. These include applying 95% (rather than the customary 90%) CI to AUC and Cmax while retaining the 80-125% acceptance limits, narrowing the acceptance limits for AUC to a range less than 80-125%, applying 'individual bioequivalence' concepts or by developing individual guidances that are drug specific. Drug specific guidances should base acceptance limits on the potency, concentration - effect (therapeutic and safety) relationship and intrasubject variability of the drug product. It was noted that bioequivalence standards, although primarily used for the evaluation of generic products, are also used to evaluate innovator products when they are reformulated or when other significant manufacturing changes are made. Therefore, imposing tighter controls has implications for both the generic and innovator drug industries.

By definition, NTR drugs exhibit small intrasubject variability so it is quite likely that they would be able to meet an acceptance limit of 80-125%. As previously stated⁵, if NTR drugs did not have inherently small intrasubject variability, patients would experience cycles of toxicity and lack of efficacy and therapeutic drug monitoring would be useless.

The 'pros and cons' of narrowing the acceptance range for AUC were discussed. Narrowing the acceptance range would likely increase the number of subjects required in order to show bioequivalence which would lead to increased cost to manufacturers and, eventually to patients (5). Lastly, narrowing the range would serve to satisfy those that call for a tighter interval and this is inconsequential (5). Arguments for tightening of the

acceptance limits were also noted and they are that inherently, NTR drugs have less intrasubject variation so although the number of subjects required would likely be more than a conventional bioequivalence study, the number should not be prohibitive (5). Well designed dosage forms should not have trouble meeting tighter standards (5). In addition, a narrower range would have an important placebo effect on clinicians and patients perhaps diminishing concerns about the interchangeability of different brands (5).

The issue that Cmax and AUC, although the classic metrics for determination of rate and extent of absorption of a drug product, do not provide any information on the 'shape' of the curve or the 'input-time' profile of a drug was discussed. Narrowing the acceptance range may result in enhanced 'superimposability' of the plasma concentration curves of two products and may address concerns over 'shape' and 'input-time'. These may be important considerations when one considers the potency of certain drugs that fall under the definition of NTR drugs. Concern was expressed that it may not be reasonable to treat all drugs defined as NTR drugs the same, but rather, individual guidances should be developed based on intrasubject variability, potency and the concentration-effect (therapeutic and safety) of an individual drug.

The comment was also made that perhaps the way these issues will eventually be dealt with will be from a legislative or policy perspective. State Legislatures and Boards of Pharmacy in the USA have considered proposals that would place additional requirements on dispensing prescriptions for drugs that are termed NTR (4). Requirements that have been suggested include obtaining the documented consent of the prescriber and the patient before dispensing a generically equivalent drug product that is different from the product indicated on the prescription (4). Governments may have no choice but to impose stricter controls on NTR drugs due to strong public lobbying groups such as The Health Alliance for NTI (narrow therapeutic index) patient safety. Apparently, this is a growing national coalition in the USA, dedicated to the protection of the millions of Americans who take one or more NTR drugs.

DISCUSSION AND SUGGESTIONS

The following are a series of concerns that were discussed and deliberated. The group felt these concerns should be addressed prior to the implementation of bioequivalence standards for NTR drugs. A brief explanation of the rationale follows each concern.

Concern #1:

The definition that a NTR drug is one in which the ratio of the lowest concentration at which clinical toxicity occurs, to the median concentration providing a therapeutic effect is less than or equal to 2 does not address the 'individual' situation.

The definition, as stated, does not address instances where the 'lowest concentration at which clinical toxicity occurs' is the minimum or median concentration producing a therapeutic effect in an individual (or vice versa). The definition should be reconsidered to reflect the difficulty in managing therapeutic outcomes and potential for toxicity.

In addition, the severity of the adverse event that defines 'toxicity' is important e.g. nausea vs. hemorrhage or seizures. Perhaps the usual clinical trial definition of a serious adverse event (e.g. leads to hospitalization or death) is an appropriate definition. It is also important to define if toxicity is manifested in other organs or if it is an extension of the therapeutic effect of the drug.

Concern #2:

What is the maximum variation we could live with in a real-world situation with NTR drugs?

If a $\pm 15\%$ variation is permitted for content uniformity of a dosage form, then one must consider the range of clinically used dosage increments for the drug. Furthermore, for determination of bioequivalence if the USP allows a $\pm 15\%$ permissible variation in tablet content, this appears incongruous with a -20% to $+25\%$ variation in the regulatory

criteria. Stricter controls on manufacturing of NTR drugs may be required. The USP standard should reflect the nature of the active ingredient (i.e. NTR or highly variable drug) and not be the same for both types of drugs.

Concern #3:

Is there substantive evidence in the literature to support tighter controls for the interchange of NTR drugs?

From an evidence-based perspective, it is presently unknown if there are data in the literature to support there is a problem with the interchange of NTR drugs. It is important to search the literature to assess if these data exist. However, we cannot say with confidence that the current post marketing surveillance system is able to detect clinically significant differences between different formulations of NTR drugs. An option to finding support in the literature may be to review clinical databases or to conduct a clinical trial looking at outcomes of patients exposed to different formulations of NTR drugs.

One factor that requires further discussion is variation in intermediate outcome measurements e.g. laboratory testing and how this relates to the therapeutic outcome with NTR drugs.

Concern #4:

Comments on the draft directive 'Standards for comparative bioavailability studies involving drugs with a narrow therapeutic range - oral dosage forms' recently circulated by the Therapeutic Products Directorate, Health Canada

The group was uncertain as to the rationale behind the Therapeutics Products Directorate proposal of the bioequivalence standard of a 95% CI for AUC and Cmax at this point in time. It was felt that the decision to apply a 95% CI may be arbitrary and that rather, it would be prudent to select one or two NTR drugs and then work through the various methodological issues e.g. results of 'individual bioequivalence' vs. 'average

bioequivalence' determination. The group was also uncomfortable with the list of drugs defined by the HPB as being NTR drugs.

Because of the serious potential for toxicity, issues such as periodic bioequivalence testing between lots of innovator and subsequent-entry NTR drugs requires further discussion. *In-vitro* dissolution testing should only be used as a proxy to ensure bioequivalence is maintained if there is a significant *in-vivo/in-vitro* correlation of the drug.

The discussion was concluded by the group acknowledging that more work needs to be done to substantiate whether the small range between toxicity and efficacy for NTR drugs may actually lead to toxicity and clinical problems of lack of efficacy if these agents are substituted with inferior products. The closing sentiment was; however, that application of a general bioequivalence standard to all NTR drugs does not address drug-specific issues such as potency, variability or concentration-effect (therapeutic or safety) relationships.

ACKNOWLEDGEMENTS

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