

**OXANDROLONE (OXANDRIN) USE AND THE INTERACTION WITH WARFARIN
MECHANISMS OF ACTION AND PHARMACOLOGIC ACTIVITIES**

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I. Introduction

I am President and Founder of Longstreth and Associates, Inc. As a consultant and previously with G.D. Searle, I have specialized in assisting the pharmaceutical industry on pharmacokinetic trial design, study conduct and data analysis, product life cycle management, and generation, analysis, and utilization of pharmacokinetic and pharmacodynamic information and issues. I have a Ph.D. in Biomedical Engineering from The Johns Hopkins University, with combined studies in Clinical Pharmacology and Pharmacokinetics/Pharmacodynamics. My Curriculum Vitae is attached.

As requested I have reviewed the study report covering the oxandrolone-warfarin drug interaction study sponsored by Savient Pharmaceuticals. In my role as a clinical pharmacokineticist I have read and produced many reports of a similar nature and so am familiar with the type of question under investigation, standard study designs that try to answer that type of question, the nature of the results likely to be generated, and the methods of analysis applied to the observed data. The following document summarizes my review and evaluation of the reported results of the clinical study sponsored by Savient in order to describe the extent of the interaction between oxandrolone and warfarin. The following discusses and evaluates observations made during the study in light of the well known properties of warfarin and the various clinical interaction profiles that warfarin has with other drugs.

The following discussion starts by briefly introducing the mechanisms of action of the two drugs, oxandrolone and warfarin, before examining in sequence the three types of drug-drug interactions for which warfarin is well known. Since each of these interactions is found to be inadequate to explain the study observations, alternative explanations are hypothesized. As with any appropriate hypothesis, predictions based on the hypothesis may look good on paper, but the hypothesis needs to be tested with one or more appropriately designed studies before the hypothesis, i.e. the presumed explanation, can be used to govern decision making. In the absence of a substantiated hypothesis explaining and quantifying the source of the interaction between warfarin and oxandrolone, empirical evidence needs to be, and can be, gathered on a case-by-case basis for each oxandrolone drug product.

II. Mechanisms and Pharmacologic Activities

Oxandrolone is an analog of testosterone, the natural male androgenic hormone. As such, it is expected to have many, if not all, of the activities of testosterone. These include, but are not limited to, stimulating or suppressing the formation of sperm (the direction of the effect depends on the concentration), stimulating the formation of red blood cells, stimulating the formation of muscle tissue, and shifting the nitrogen balance. These processes involve the androgen molecule (testosterone or oxandrolone) entering the nucleus of cells and interacting with parts of the genome that start, stop and modulate the rate of synthesis of many proteins and protein precursors. The proteins that are produced,

or have their production decreased, by the presence of an androgen then interact with any of a number of cellular or tissue systems to produce effects such as those noted above.

Warfarin is a complex drug that has long been widely used as an anticoagulant. Its primary therapeutic mechanism of action is to inhibit the vitamin K dependent coagulation cascade. Vitamin K, when present, helps catalyze the conversion of inactive forms of various coagulation factors (II, VII, IX, and X and proteins C and S) to their active forms. Warfarin administration reduces the intracellular concentrations of the active form of Vitamin K so that it is no longer as available as a catalyst, and thus the coagulation factors tend to remain in their inactive configuration, even if the need for coagulation is present. The clinical manifestation of too little vitamin K and not enough active coagulation factors is prolonged bleeding in response to major and minor injuries. Administration of warfarin reduces the total active amount of the various coagulation factors synthesized by the liver, and in addition, the versions that are produced are often not fully activated and have only limited biological activity. As with most drugs, the actions of warfarin are probably not limited to the just the desired therapeutic target. However, not much research appears to have been conducted on other effects of warfarin, although it would seem reasonable that at the very least the synthesis or post-translational modification of other proteins besides the previously noted coagulation precursors might also be affected.

III. Known Mechanisms for Warfarin Interactions

A. Interaction with warfarin protein binding

Warfarin has long been recognized as prone to clinically significant drug-drug interactions. Most of these are recognized to result from the second drug interfering with warfarin's strong tendency to bind to albumin, a protein that circulates in the blood. Approximately 99% of the warfarin that is measured in a plasma sample is actually attached to albumin molecules, meaning that only about 1% of the circulating warfarin is actually free (i.e. unbound) and available to move, act or diffuse into liver cells (where it manifests its effect on coagulation factors) as blood circulates through the liver. If a second drug is administered that also binds to albumin and thereby reduces the number of albumin binding sites available to warfarin, then the amount of "free" warfarin in the circulation increases. This in turn increases the amount of warfarin available to enter the liver cells and to slow and inhibit the actions of vitamin K. A small change in the amount of protein binding, e.g. a drop from 99% to 98%, can have a dramatic effect on the amount of free warfarin. The 1% drop actually amounts to a doubling of the circulating free concentrations from 1% to 2%, and thus produces an effect equivalent doubling the amount of warfarin administered.

The pharmacological mechanism by which oxandrolone acts to affect the potency of warfarin therapy has not yet been investigated. The obvious hypothesis is to assume that oxandrolone, like many other drugs, interferes with the protein binding of warfarin

leading to increased concentrations of free warfarin and increased anticoagulant activity. Drug-drug interactions caused by interference with warfarin's protein binding are commonly encountered and the effects are predictable. For instance, once warfarin activity has been stabilized under the new conditions (for example, with oxandrolone on board), the free warfarin concentrations after stabilization will be similar to what they were before oxandrolone was added, but the total concentrations (free warfarin + bound warfarin) will be lower. The effects on protein binding might be different for the two stereoisomers of warfarin (R-warfarin and S-warfarin) so determining the actual extent in the changes in the concentrations of the combination can be relatively complex. In the study the AUCs (an overall measure of concentration exposure) for total R-warfarin, total S-warfarin and the combination of total R+S-warfarin all were lower in the presence of concomitant oxandrolone than when oxandrolone was not present. This particular result is consistent with a decreased protein binding in the presence of oxandrolone. Free warfarin concentrations were not measured during the study so the prediction of no change in that parameter cannot be evaluated.

Another effect expected from a drug-drug interaction that reduces protein binding is an increased rate of elimination for warfarin. This is the result of an increase in the clearance of total drug secondary to an increase in the fraction of the circulating warfarin that is not bound to albumin. An increased elimination rate for warfarin leads to a shortening in the warfarin elimination half-life. This prediction is the opposite of what was actually observed in the study with oxandrolone. In the study both R-warfarin and S-warfarin showed increases in elimination half-life, rather than the shortening predicted assuming the drug-drug interaction was mediated by protein binding. Therefore altered protein binding alone is not a suitable explanation for the oxandrolone-warfarin interaction, and dosing corrections made in the clinical setting based on that premise will be inappropriate.

B. Interaction with warfarin metabolism

A second very common mode by which drugs interact is for one drug, or both, to affect the rate of metabolism of the other, and thus to alter how fast one or both drugs are removed from the body. Warfarin is reported to be nearly completely absorbed from the gastro-intestinal tract after oral administration. However, it is partially metabolized in the liver during its first pass through the liver on its way from the gut (where the tablet was absorbed) to the general circulation. R-warfarin is reported to be primarily metabolized by the metabolic enzymes named CYP 1A2 and CYP 2C19, whereas S-warfarin is reported to be primarily metabolized by the metabolic enzyme named CYP 2C9. When two molecules compete for the same metabolic pathway, the usual result is that sharing the metabolic pathway leads to the metabolism of both molecules being slowed relative to what would occur if either was present alone. Therefore, if warfarin is one of these molecules and oxandrolone the other, their competition for one or more of the metabolic enzymes will result in a slowed elimination and prolongation of the warfarin half-life. In addition, the associated decrease in the first pass metabolism would increase the

circulating warfarin concentrations (increase the AUC) if the dose was maintained the same. Alternatively, the warfarin dose could be reduced in the presence of warfarin in order to keep concentrations and effects in the desired range. Alterations in the metabolism do not affect the activity of the drug, and a drug-drug interaction based on metabolic interference is predicted to result in equal anticoagulant activities as long as the drug concentrations (i.e. AUCs) are similar. However, smaller warfarin doses will give those equivalent concentrations (and AUC) when the interfering drug is present.

Consistent with expectations for a metabolic interaction, warfarin doses in the study did need to be lowered when oxandrolone was present. Also, as predicted from the slowed metabolic elimination, the warfarin elimination half-life was observed to increase. However, the prediction that the equal anticoagulant effect would be the result of equal warfarin blood concentrations was not observed. Since the concentrations of both R-warfarin and S-warfarin were substantially lower when oxandrolone was present compared to when it was not present,

an explanation based on slowed metabolic clearance is inadequate. Therefore metabolic inhibition is not a suitable explanation for the oxandrolone-warfarin interaction, and dosing corrections made in the clinical setting based on that premise will be inappropriate.

C. Interaction with the absorption process

Another class of drug-drug interactions that has received increased attention in recent years is interactions resulting from one drug affecting the rate or extent of absorption of a second drug from the gastrointestinal tract following the swallowing of a tablet or capsule. The usual result in this type of interaction is that administration of the combination of the two drugs leads to a greater fraction of one or both of the drugs reaching the systemic circulation than if the drugs were being used as just single agents.

The obvious way to compensate in the clinic for this increased absorption is to administer less drug. In this way a targeted blood concentration can be attained, and the desired effect will be closely tied to that targeted concentration.

However, warfarin is known to be essentially 100% absorbed when administered alone, so it is not possible for a second drug to further increase the fraction of the warfarin dose that is absorbed. Therefore this potential mechanism can be ruled out as playing a role in the warfarin-oxandrolone interaction. Furthermore, since it was observed that a smaller warfarin dose was required to produce the targeted anticoagulant effect when oxandrolone was present compared to when it was not, we can also rule out the more unusual type of absorption based drug-drug interaction where the addition of a second drug actually reduces the extent of absorption of the first drug. (Note: The case where the absorption remains unchanged, i.e. at about 100%, but the extent of first pass metabolism, and therefore the fraction of the dose reaching the blood stream is reduced by oxandrolone, was considered in the preceding metabolic interaction section.)

!V. Hypothesized Mechanisms for Warfarin Interactions

A. Altered Pharmacodynamics

As noted near the beginning of this discussion, oxandrolone has a mechanism of action that involves modulation of protein synthesis, while warfarin's known mechanism of action involves the modification of proteins after they have been synthesized. By reducing the activity and amount of vitamin K, warfarin alters the rate and extent of the catalytic conversion of coagulation factors from inactive forms to one or more versions of the active, or partially active, forms. Thus, both oxandrolone and warfarin have effects on protein quantity and protein activity, although they act at different places in the "life cycle" of proteins. In general, oxandrolone and warfarin do not act on the same proteins, but there may be some overlap.

Whether warfarin affects proteins other than those found in the coagulation cascade is not known, but based on historical experience with almost all other drugs, total inactivity outside that small sub-category of proteins is unlikely. Similarly, testosterone, and therefore probably oxandrolone, has profound effects on a wide variety of body systems including muscle formation, red blood cell formation, sperm production, and mood elevation. Given this very broad spectrum of actions it cannot be assumed that oxandrolone has no impact on the production of any protein that also falls within the sphere of influence of warfarin. Interactions of this type are termed pharmacodynamic interactions (as distinguished from the pharmacokinetic interactions discussed above).

Pharmacodynamic interactions are the most difficult to study, evaluate and prove. In practice, they are often identified by the elimination of other possibilities, such as those discussed above. However, just invoking the existence of a pharmacodynamic interaction is not an answer in itself. There are such a large number of ways that the pharmacodynamics can be altered that no general predictions can be made as to how patterns will be altered in specific instances, for instance warfarin and oxandrolone, without knowing the actual details of the pharmacodynamic interaction. Commonly invoked pharmacodynamic interactions are competition for receptors, modulation of receptor sensitivity, increasing or decreasing the number of receptors available, altering the availability of a precursor molecule, altering the rate of synthesis or destruction of critical enzymes, carriers or receptors, and altering gene expression and/or protein turnover.

Pharmacodynamic mechanisms typically cannot be discovered using clinical trials. They require numerous studies in model systems, and the testing and elimination of several proposed hypotheses. Without specific knowledge of the source and extent of a pharmacodynamic interaction, clinical comparisons require case by case evaluation for each oxandrolone drug product.

B. Combinations of pharmacokinetic interactions

As noted above, no single commonly encountered drug-drug interaction is consistent with the observations in even the single study that is under discussion. Each of the suggestions has at least one predictable outcome violated by the study observations. The next step, logically, is to evaluate whether a combination of two or more of the previously proposed interaction mechanisms might improve the match between prediction and observation.

A reasonable candidate for a combination interaction is for oxandrolone to both interfere with warfarin protein binding and to decrease warfarin metabolism. Directionally, in the presence of oxandrolone the required warfarin dose to produce a given effect should go down, the warfarin half-life should be prolonged, the apparent "sensitivity" to warfarin should be increased, and the overall exposure to warfarin (the AUC) should be less. All these events were observed in the oxandrolone-warfarin interaction study. However, directional consistency is not the same as qualitative or quantitative success. This combination mechanism is an hypothesis, that is, it is just a possible explanation, and probably one of many possible explanations. It should not be assumed to be true until it is tested and challenged by appropriate experiments.

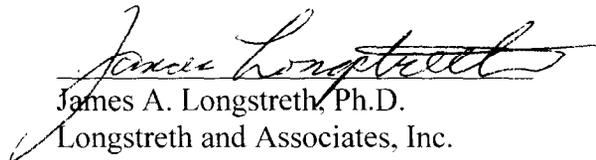
In the opinion of this reviewer, it is very probable that the combination mechanism proposed above will also prove to be insufficient to explain the study observations. This conclusion is based the knowledge that testosterone, the molecule which oxandrolone mimics, has profound effects on the synthesis rate and turnover rate of many proteins at the level of gene expression. I am unaware of any reports of warfarin acting on gene expression, but it does exert its anticoagulant effect by altering the post-translational modification of proteins. Thus there is an obvious setting for a pharmacodynamic interaction to occur, with oxandrolone altering the size and possibly even the nature of the precursor pool of proteins whose conversions are catalyzed by vitamin K, and vitamin K activity in addition being modulated by warfarin. As indicated above, only experimental approaches can help identify the correct, or most appropriate, mechanism or combination of mechanisms. Thought experiments are useful for directional evaluation, but they are not capable of providing sufficiently strong outcomes to substitute for clinical experience. Dosing corrections made in the clinical setting based on the presumed, but untested, details of an interaction may lead to inappropriate dosing in some settings.

V. Summary

The drug-drug interaction that has been reported between oxandrolone and warfarin is superficially similar to many well known warfarin interactions. However, when examined for consistency, the clinical and pharmacokinetic observations in the case of oxandrolone and warfarin violate at least one expected outcome for each of the traditional explanations. Consideration of more complicated mechanisms (pharmacodynamic or combinations) suggests that rational explanations for the observed behavior can be found, but that at the current time there are too many possibilities and too little information to

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select the appropriate explanation. It is not clear at this time how the rate and extent of oxandrolone and warfarin availability interact, which parameters can be used to assess the extent of the interactions, or whether the effects are fundamentally pharmacokinetic or pharmacodynamic in nature. Therefore, any proposed explanation at this time needs to be regarded as an hypothesis, and subject to experimental evaluation.


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EDUCATION:

B S. (with Honors, summa cum laude) in Chemical Engineering, Univ. of Iowa, Iowa City, Iowa.

Ph.D. in Biomedical Engineering, The Johns Hopkins University, Baltimore, Maryland.
(Combined studies in Biomedical Engineering and Clinical Pharmacology in
Pharmacokinetics/Pharmacodynamics)

EXPERIENCE:

- 1997-present Founder and President, Longstreth and Associates, Inc , Mundelein, IL, and
2000-present Executive Director Clinical Affairs, CanReg, Inc., Mundelein, IL and Dundas, Ontario.
Consultant to the pharmaceutical industry on pharmacokinetic trial design, study conduct
and data analysis; production of regulatory submissions; strategic utilization of
pharmacokinetic information, and product life cycle management
- 1994-1997 Director, Strategic Development, G D. Searle, Skokie, IL
Managed technology/clinical portions of patent expiry, line extension, technology
acquisition, and competitive assessment projects
- 1993-1994 Director, Corporate Clinical Research, G.D. Searle
Coordinated comparator and market support studies, managed regulatory awareness
projects
- 1991-1993 Director, Clinical Pharmacokinetics, G D. Searle
Coordinated pharmacokinetic/pharmacodynamic programs for in-licensed and marketed
products
- 1989-1991 Associate Director, Clinical Pharmacokinetics, G D. Searle
Conducted and supervised pharmacokinetic/pharmacodynamic projects for in-licensed
and marketed products
- 1988-1989 Senior Clinical Research Scientist, Clinical Pharmacokinetics, G D. Searle
Designed and conducted pharmacokinetic/pharmacodynamic studies for in-licensed and
marketed products
- 1983-1988 Assistant Professor, Division of Pharmaceutics, School of Pharmacy, University of North
Carolina, Chapel Hill, NC.
Taught undergraduate pharmacokinetics; supervised graduate student research projects
- 1982-1983 Fellow - Division of Clinical Pharmacology, Department of Medicine, The Johns Hopkins
Medical Institutions, Baltimore, Maryland.
Supported Phase I and Phase III clinical research programs
- 1969-1971 Commissioned Officer - United States Public Health Service, Chemical Engineering
Section, Biomedical Engineering and Instrumentation Branch, Division of Research
Services, National Institutes of Health, Bethesda, Maryland
Provided programming support for pharmacokinetic modeling research in oncology

PROFESSIONAL RESPONSIBILITIES:

1997-present: President, Longstreth & Associates, Mundelein, IL

Consultant to the pharmaceutical industry for identifying and implementing technology, clinical, and regulatory strategies for product registration and product life-cycle management, for the design, conduct and analysis of pharmacokinetic and pharmacodynamic studies in support of regulatory submissions; and for the generation and evaluation of development strategies.

Recent projects include analysis and writing of pivotal pharmacokinetics reports; protocol development, placement and supervision of Phase I/II trials; writing Biopharmaceutical and Pharmacokinetic sections and Clinical Pharmacology sections of NDA submissions; capabilities audits of bioanalytical sites; and development of expert reviews of journal articles and recent pharmacokinetic literature for submission to regulatory agencies and formulary review boards.

1994-1997. Director, Strategic Development, G.D. Searle, Skokie, IL

Responsible for managing projects and coordinating selected regulatory, clinical, and technology acquisition strategies within the Cardiovascular, Arthritis, Oncology and Women's Health franchises. Responsible for developing and coordinating the technology and clinical portions of line extension and regulatory strategies for brand support of leading marketed product lines. Designed and manage competitive intelligence initiatives focused on core technologies and selected regulatory issues, that draw on trade publications, the financial community, scientific meetings and publications, professional networking, and internal and external experts. Responsible for acquiring and structuring product assessments from market research, product managers, R&D project teams, and Discovery project teams on a global basis to incorporate into the decision management and commercial value models.

1993-1994. Director, Corporate Clinical Research, G.D. Searle

Responsible for implementing Phase IV clinical programs to support marketed products, for designing and implementing development strategies for line extensions and new indications for marketed products. Produced documents for, and participated in scientific interactions with state, federal and international regulatory agencies for IND, NDA, ANDA and the equivalent international submissions.

Developed and coordinated a successful, precedent setting SNDA (line extension) submission to the FDA based on documented pharmacokinetic/pharmacodynamic correlations, as opposed to relying on the usual two clinical trials. Designed and coordinated execution of the pharmacokinetic package supporting the successful registration of the first cardiovascular product exploiting cardiovascular chronopharmacology.

1991-1993 Director, Clinical Pharmacokinetics, G.D. Searle

Responsible for budgeting, design, coordination, and analysis of pharmacokinetic, pharmacodynamic, population pharmacokinetic, and biopharmaceutics studies in Phases I-IV for in-licensed and marketed compounds. Developed and directed a novel pharmacokinetics development strategy for a prototype drug with multiple active stereoisomers. Produced written documentation and made oral presentations on pharmacokinetic and pharmacodynamic data packages for assorted scientific interactions with US and international regulatory agencies (e.g., FDA, HPB, CSM, CPMP) for IND, NDA, ANDA and the equivalent international submissions. Developed and made presentations conveying pharmacokinetic and pharmacodynamic data and arguments to state formularies, groups of investigators, market planning colleagues, company sales groups, and major customers.

Approvals were obtained, and labeling successfully negotiated, for antibiotic and NSAID NDAs (and their ex-US equivalents) which contained pharmacokinetic and biopharmaceutics sections written by myself or my direct reports.

1989-1991: Associate Director, Clinical Pharmacokinetics, G.D. Searle

Responsible for the design, coordination and analysis of pharmacokinetic, pharmacodynamic, and biopharmaceutics studies in Phase I, Phase II and Phase IV for in-licensed and marketed compounds. Compiled and wrote the pharmacokinetic and biopharmaceutics portions of a successful antibiotic NDA submission. Developed the pharmacokinetic portions of draft

PROFESSIONAL RESPONSIBILITIES (continued):

1988-1989 Sr Clinical Research Scientist, G D Searle
Responsible for the design, coordination and pharmacokinetic analysis of Phase I, Phase II and biopharmaceutics studies

1983-1988 Assistant Professor, Division of Pharmaceutics, School of Pharmacy, University of North Carolina, Chapel Hill, NC
Responsible for organizing and teaching undergraduate and graduate courses in pharmacokinetics and pharmacodynamics. Responsible for mentoring Masters students and Ph D. candidates and for guiding their dissertation research

1982-1983: Fellow - Division of Clinical Pharmacology, Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

1969-1971: Commissioned Officer - United States Public Health Service
Stationed with the Chemical Engineering Section, Biomedical Engineering and Instrumentation Branch, National Institutes of Health, in Bethesda, Maryland

OTHER PROFESSIONAL ACTIVITIES:

Continuing Medical Education – Presenter at Endocrine Society CME programs on testosterone replacement therapies and exploitation of testosterone pharmacokinetics by new product technologies.

Member, Board of Directors, of RETT and of RegenaCorp (a start-up company with proprietary high throughput technologies, and a start-up pharmaceutical company with proprietary wound-healing technologies, respectively)

US Patent 5,955,500 Pharmaceutical Compositions Containing Non-racemic Verapamil and Process for Optimizing the Pharmaceutical Activity of R- and S-Verapamil Sept. 21, 1999.

Workshop Presentation, Managing the Patent Expiration Dilemma, Pharmaceutical Executive Conference, Oct 28-29, 1997.

Adjunct faculty member (Lecturer in Medicine), Committee on Clinical Pharmacology, University of Chicago, Chicago, Illinois. (1994-1997)

Member, Planning Committee for 4th International Symposium on Chiral Discrimination September 19-22, 1993 Montreal, Quebec

Organizer of, and participant in, the Symposium at the Annual Meeting (Oct. 1991) of the American College of Clinical Pharmacology entitled "From Controversy to Resolution: Bioequivalency of Chiral Drugs"

Organizer of, and participant in, the Symposium at the Annual Meeting of the American College of Clinical Pharmacology (Nov 1990) entitled "The Clinical Pharmacology of Lomefloxacin: A New Difluorinated Quinolone Antibiotic"

PROFESSIONAL ORGANIZATIONS AND AFFILIATIONS:

American Association for the Advancement of Science
American Association of Pharmaceutical Scientists
American Society for Clinical Pharmacology and Therapeutics
Canadian Society for Pharmaceutical Sciences
Drug Information Association
National Association for the Self-Employed
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Society for Values in Higher Education
Tau Beta Pi

PUBLICATIONS:

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