RECENT ADVANCES IN

DRUG DELIVERY SYSTEMS

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FOREWORD

The evident rapid expansion of scientific work and intense interest in both experimental and clinical aspects of new drug delivery systems provided strong motivation for planning this symposium. In designing the program, speakers were identified for their particular expertise in a wide range of topics such as dermal delivery systems, pro-drugs, oral prolonged release, rate-controlled drug delivery, the pharmacokinetics of drug release systems, the synthesis of polymeric drug carriers and the refinement of drug delivery pumps. Because of the considerable involvement of diverse scientists from laboratories around the world where investigations relevant to the topic are now being pursued, a deliberate effort was made to invite international leaders in the field to share their knowledge and experimental outcomes. Thus, plenary papers and panel discussions were offered by organic chemists, bioengineers, pathologists, material scientists, physical chemists, and pharmacokineticists from academic and industrial laboratories in some dozen countries.

This book which records the presentations offered at the symposium covers a broad array of topics ranging from general overviews of the physicochemical concepts and analytical methodology which underpin the refinement of drug delivery systems and the tissue responses associated with the use of such systems through detailed discussions of a variety of current approaches employed in the development of new systems. Examples of such presentations include the use of albumin microspheres as carriers of cytotoxic and therapeutic agents; advances in the preparation of oligomers and polymers as drug carriers; progress in the refinement of implantable insulin pumps and self-regulating insulin delivery systems; and the use of polymer coated liposomes as well as magnetic microspheres, magnetic beads and oscillating magnetic fields to achieve targeted drug delivery to specific organs. Considerable additional attention is directed toward the kinetics of drug release from biodegradable microcapsules, polymer membranes, and matrix devices.

In perusing these pages, several common threads are likely to be apparent. First, it is obvious that advances in the area are occurring at a rapid and accelerating pace and that these advances have the potential to bring us closer to achieving a greater degree of pharmacologic selectivity than has been heretofore attainable (Goldman, P., Rate-controlled drug delivery. N. Engl. J. Med., 307: 286-290 (1982)). However, it is equally clear that much remains to be done if that laudable potential is to be realized. Considerable gaps still exist in our understanding of the biological and cellular rationale involved in targeting drugs to specific organs and tissues. Finally, and perhaps most importantly, ultimate success in transferring the significant progress which is detailed in this volume to the complexities of the therapeutic arena, will undoubtedly require the committed interdisciplinary effort of researchers with widely diverse scientific backgrounds who are willing to continue to share their expertise in collaborative efforts involving both academia and the private sector.

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PREFACE

Utilizing conventional drug delivery systems, delivering the desired amount of drug to a specific site to produce a beneficial pharmaceutical response is rarely satisfactorily achieved. Until recently, drug administration methods for the treatment of disease have remained virtually unchanged, i.e., oral ingestion of tablets/liquids, topically administered ointments, injections of suspensions/solutions.

During the past years, many investigators have engaged in the research and development of controlled release drug delivery systems. Release rates in these systems are regulated by a device designed to provide an accurate and predictable release of drug. The insertion of such a device in close proximity to the desired site of drug action greatly enhances the accuracy of delivery and rate of release. Conventional methods utilizing controlled release systems in which a general systemic drug release is achieved can minimize side effects due to the controlled release rates provided by such systems.

Exciting, novel research in this area promises the development of drug delivery systems capable of providing precise and predictable drug release rates with greater efficacy and minimal side-effects. These phenomenal new developments can be attributed to research advances made in the fields of polymer chemistry, physical chemistry, pharmacology, bioengineering and pharmaceutics. It is important to recognize the interdisciplinary nature of the effort required to create controlled release drug delivery systems. The physicochemical properties of both polymer and drug are important factors in the design of a controlled release delivery system to produce a desired release rate. In addition, the toxicity, biocompatibility and immunogenicity of the delivery systems are critical due to the interfacing of the devices directly with the biological environment in which they are injected, implanted or inserted.

This symposium was organized primarily to provide an opportunity to bring together a group of internationally recognized researchers representing the frontiers of their respective fields to present on a broad range of topics covering both the physical experiments and clinical aspects of new drug delivery systems. Although international

in scope, the symposium was organized to provide an interdisciplinary approach.

This proceeding deals mainly with issues related to state-of-the-art basic research and drug delivery system design. Current advances in drug release devices composed of hydrophobic hydrogels and biodegradable polymers are discussed in this publication; additional subjects covered are delivery systems designed for specific targeting, physical and chemical pumps, and novel dermal and oral drug delivery systems.

Working together organizing this symposium, from the inception to its successful completion, was an enjoyable experience. We deeply appreciate the efforts and encouragement of Dean Harold H. Wolf and Professor William I. Higuchi. We also thank Ms. Dana Feiler and Ms. Suzanne Winters, Symposium Coordinators, for their immense contribution. Finally, we extend our appreciation to the contributors and participants whose efforts ensured the success of the symposium.

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CONTENTS

TOPICAL DELIVERY OF ANTIVIRAL AGENTS: IN VIVO/IN VITRO CORRELATIONS

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ABSTRACT

There has been significant progress made during the past ten years in our understanding of drug transport processes in skin and the use of this information in topical and transdermal drug delivery. Physicochemical concepts and methods have been especially valuable in this regard. We have recently developed a method which combines in vitro experiments with hairless mouse skin and theoretical techniques based upon physical chemical relationships for predicting target-site levels of drug delivered by the drugs or prodrugs in various vehicles. A three-layer model was developed (stratum corneum, epidermis and dermis) and validated by independent experiments. In our most recent investigations, target-site predictions were made for the 5'-monoester prodrugs of vidarabine (an antiviral agent) delivered topically into hairless mouse skin with and without the penetration enhancer, Azone (dodecylazacycloheptan-2-one). The 5'-valerate ester of vidarabine was predicted to be the best among five monoester prodrugs. It was, nevertheless, predicted to be only marginally effective (against herpes virus) in sustaining high enough steady-state vidarabine levels in the epidermis when delivered from conventional creams. Efficacy predictions for the 5'-valerate in formulations containing 10 to 20% Azone, suggested that the Azone formulations would be able to sustain much higher steady-state epidermal vidarabine levels (50 to 200 X). The first set of in vivo studies by Dr. W.M. Shannon completed very recently showed that topical treatment with the 5'-valerate prodrug of vidarabine in a conventional cream was only marginally effective in reducing lesion scores and the mortality

rates of prodrug of vidarabine in a conventional cream was only marginally effective in reducing lesion scores and the mortality rates of hairless mice infected topically by Herpes Simplex Virus Type I. With Azone in the formulations, the lesion scores were significantly improved and the mortality rate was zero.

INTRODUCTION

Recently (1,2-6,7,8) a method was developed for predicting the steady-state levels of drug in skin delivered topically by a prodrug. The method combines *in vitro* diffusion experiments with skin (or components of skin) and physico-chemical calculational techniques for handling the simultaneous diffusion and metabolism problem. In an application of this method, the ability of the 5'-monoesters of vidarabine (an antiviral agent) to deliver vidarabine into the epidermis of the hairless mouse skin was investigated. The analysis (7,8) suggested that the 5'-valerate ester of vidarabine may be the most effective among the vidarabine prodrugs in this homologous series; however, because of the extreme barrier nature of the stratum corneum, it was concluded that the 5'-valerate topically applied as a suspension (for maximum driving force purposes) may still be only marginal with regard to therapeutic efficacy in cutaneous herpesvirus infections in hairless mice.

In a very recent *in vitro* study (9,10) Vaidyanathan, Flynn and Higuchi showed that the skin penetration enhancer, dodecylazacycloheptan-2-one (Azone), incorporated as an additive in the formulations greatly increased the transport rates of vidarabine and the 5'-valerate ester of vidarabine in the stratum corneum of the hairless mouse. Vidarabine species transport rates of 50 to 500-fold greater than without Azone were observed in these experiments and these results immediately suggested the desirability of conducting *in vivo* efficacy studies examining the influence of Azone on the topical treatment of cutaneous herpesvirus infections in hairless mice. The present report describes the results of our first *in vivo* experiments with Azone.

EXPERIMENTAL

Candidate antiviral agents against HSV type 1-induced cutaneous infections in hairless mice were evaluated using the procedures described by Lieberman, Schafer and Came (11) as modified by Klein, Friedman-Kien, and Brady (12).

Virus

The HS-123 strain of herpes simplex virus type I described above was employed in these studies. The virus was propagated and

assayed in Vero cells grown as monolayer cultures and stock virus pools were stored frozen at -70°C.

Mice

HRS/J strain hairless mice, 15-20 g, were obtained from Jackson Laboratories (Bar Harbor, Maine) and were segregated in groups of six.

Infection of Mice

Mice were lightly anesthetized with ether and the lumbar area was scratched six times with a 26-gauge needle in a cross-hatched pattern. The virus suspension was then applied to the abraded area by rubbing approximately 0.05 ml (10 LD_{50}) of virus dilution on the scratched surface of the skin for 10 seconds. This resulted in a 100% infection and mortality rate in the inoculated animals. Mice were examined daily for 14 days and the lesions were scored according to the scoring method of Lieberman et al. (11). The mean lesion scores were determined daily and the average peak lesion score was determined at the end of the observation period from the maximum score attained by the mice, irrespective of the day on which it was recorded. Lesions were scored from 0 to 4.0 using the following scale: 0 = no lesion; 0.5 = several discrete punctate lesions or a lesion <5 mm in length; 1.0 = lesion 5-9 mm; 2.0 = lesion 10-19 mm (classified as severe); 3.0 = lesion 20-29 mm; and 4.0 = lesion >30 mm in length. When the lesion was bilateral ("banding"), the longer epidermal band was scored.

Antiviral tests

For treatment, candidate antiviral agents were administered to HSV-1-infected hairless mice by the topical route. A group of 12 mice served as virus controls while groups of 6 virus-infected animals received each of the test compounds in a 10% ointment, twice a day for 5 days, starting 4 hours after virus inoculation. Groups of three uninfected animals were treated with each of the drug concentrations and served as drug-treated controls. Three animals were held as normal, placebo-treated, uninfected controls. The effects of topical treatment with a known active antiviral (acyclovir) were assessed and compared with results obtained with the candidate materials.

The significance of the differences observed in survival rate and number of animals developing lesions was determined by the Chi-Square Test. The mean survival time differences were evaluated by the Student t-test.

RESULTS (TABLE 1) WITH AraA and Ara-A-5'-MONOVALERATE

Among untreated or placebo-treated mice inoculated with HSV-1, lesion scores of 4.0 were obtained in all animals and the mortality rate was 100%. Topical treatment with 10% araA (the parent drug) alone was of no benefit to the therapy of these cutaneous infections. Treatment with 10% araA + Azone™, however, decreased the peak mean lesion score to 2.7, resulted in a significant ($p<0.05$) reduction in mortality, and caused a significant ($p<0.05$) increase in the mean survival time, but no significant effect on peak mean lesion score or mortality. However, if 10% araAMV was applied with Azone™ in the formulation, all animals survived. Treatment with 5% acyclovir alone was effective in significantly reducing the peak mean lesion score (to 2.4) and in preventing death, but treatment with 5% acyclovir + Azone™ was markedly effective in preventing the development of HSV-1-induced skin lesions (peak mean lesion score = 0.1) and in preventing death. Azone™ alone appeared to have a slight effect on viral pathogenesis and caused an increase in the mean survival time. However, the peak mean lesion score and observed mortality rate was not statistically different from that of the untreated or placebo-treated controls.

DISCUSSION

Although these are preliminary results and repeat of these studies are necessary, they are very exciting. The predictions based upon the combined in vitro experiments and model calculations are very consistent with these in vivo experiments.

AraAMV (without Azone) was predicted (1,6-8) to be only marginally effective and the data in Table 1 for AraAMV alone are consistent with this. There was a highly significant increase in the mean survival time with AraAMV, but no significant effect on peak mean lesion score or mortality.

AraAMV with Azone greatly enhances the Ara-A flux and therefore, the steady-state Ara-A levels in the epidermis (9,10). The data in Table 1 show that the maximum average lesion score was greatly improved with AraAMV with Azone and the mortality rate was zero in this case.

The treatment with Ara-A with Azone was also predicted to be much more effective than Ara-A alone (9,10). The data show that Ara-A with Azone resulted in an improved mean lesion score, a significant reduction in mortality and a significant increase in the mean survival time.

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Table 1. Effect of Topical Treatment with Antiviral Drugs Alone and in Combination with Azone™ on HSV-1 Skin Infections in Hairless Mice

Group	Maximum Average Lesion Score	No. of Mice with Lesions/Total	Mortality Rate (No. Dead/Total)	Mean Survival Time (in Days)[b]
Untreated Control	4.0	6/6	6/6	6.3
Placebo-treated Control	4.0	6/6	6/6	6.8
10% Ara-A	4.0	6/6	5/6	7.4
10% Ara-A + 15% Azone™	2.7	4/6	3/6*[c]	8.0*
10% Ara-AMV	4.0	6/6	5/6	9.0**
10% Ara-AMV + 15% Azone™	2.6	6/6	0/6*	-
5% Acyclovir	2.4	5/6	0/6*	-
5% Acyclovir + 15% Azone™	0.1	1/6*	0/6*	-
15% Azone™ Alone	3.4	6/6	4/6	9.5*

[a]Drugs were administered topically, b.i.d for 5 days, beginning 4 hours after virus inoculation.

[b]Only animals dying on or before day 14 postinfection were considered in the calculation of the mean survival time.

[c]Probability that the observed decrease in the number of mice with lesions/total (χ^2-test), the observed decrease in the mortality rate (χ^2-test), or the observed increase in mean survival time (Student t-test) was due to chance: *$p<0.05$; **$p<0.005$.

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