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RESEARCH ARTICLE

RECENT ADVANCES IN VETERINARY PHARMACOLOGY

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Abstract

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Introduction

While exactly not predicting the future, this is an attempt to provide an insight in to some possible developments in Veterinary Pharmacology over next decade. Science is moving too rapidly so we need some authoritative marker against which to assess progress. The main objective of this topic is to make an educated guess as to what veterinary pharmacology will look like in next decade?

By examining the past, it is evident that change is incremental unless a transforming discovery occurs. In the last few decades, such events have dramatically changed medicine and pharmacology, however they have not percolated through the system to the effect that novel drugs have replaced our traditional armamentarium. There are five transforming technologies i.e.:

1. Continued advances in computer technology
2. Nanotechnology
3. High-throughput screening
4. Control and targeted drug delivery
5. Pharmacogenomics

These five technologies having a great impact on veterinary therapeutics & will shape up the future of veterinary pharmacology. These should lead toward more efficacious and safer drugs across most therapeutic classes due to both increases in our knowledge base as well as more efficient drug development.

What may have even greater impact is the integration of more than one of these trends to yield increasingly novel products and development strategies. This also increases the complexity of predicting what will emerge in next decade from an intersection of multiple independent pathways. Combined products (drug and delivery device, implanted physiological feed-back systems, nanoparticle drug carriers) require regulatory decisions to be made concerning whether the parts of a system or its whole should be evaluated. What is the safety of residues from an implanted drug carrier or delivery technology? How stable and robust are the embedded mathematical algorithms? Can owner miss-use of a new product result in danger to either the pet being treated or to the owners themselves? Should novel manufacturing methods introduce a change into how a drug's safety is assessed?

1. Continued advances in computer technology

One of the most pervasive changes that have highly impacted all aspects of pharmacology is the continued development of computer technology, not least in terms of speed of processing, amounts of data that can be economically handled, and integration of previous separate systems that allow automation of processes and devices previously thought impossible only a decade ago. The portability of diverse software systems on different computing platforms has accelerated the development of numerous systems that have great impact on both the processes of drug discovery development and approval. Parallel advances in the sophistication and "user-friendliness" of pharmacokinetic modeling software coupled with the further development of pharmacodynamic models, allows an increased throughput in conducting ADME and explorative studies that in the past were time and cost prohibitive. Of more importance, this increased ability to conduct such studies, using techniques which can be grouped under the umbrella of the term *pharmacometrics* (Ette and Williams, 2007), increases our understandings of the biological determinants of ADME processes and gives us the ability to begin developing structure-activity relationships (SAR) for both ADME and pharmacodynamic endpoint.

This can be taken further by integrating genomic and proteomic data with PBPK models to create systems biology approaches which attempt to describe chemical action by building models from the receptor to the whole animal. Such models are in the early stages of development, however, and as they become more developed, they will have the potential to dramatically advance the field of comparative pharmacology and toxicology with the resultant increase in more targeted drugs with better safety profiles. Once validated, they would allow so-called "in silico trials" (simulations done entirely on a computer) to be conducted which potentially could develop lead drug compounds using dramatically fewer preclinical laboratory animal studies. Of course, a small number of more targeted live animal studies would still have to be conducted before approval, but these would be reduced in number due to the efficiency and accuracy inherent to the robustness of the in silico analysis coupled to the automated battery of preclinical safety and efficacy tests.

The final area where computational power has had a major impact is in the application of more sophisticated statistical tools to analyze these ever increasing sets of in The final area where computational power has had a major impact is in the application of more sophisticated statistical tools to analyze these ever increasing sets of integrated data. In the field of pharmacology, so-called population pharmacokinetic models are beginning to be used to define the population factors that determine drug disposition and activity (Ette and Williams, 2007). In order for successful products to be developed, the determinants of individual and subgroup susceptibility must be defined. Population pharmacokinetic models allow the integration of kinetic models describing ADME parameters to be linked to statistical models defining where variability in a population response occurs.

These models hold promise to identify factors such as age, disease or breed which significantly modify drug disposition or activity.

2. Nanotechnology

Another transforming technology that has promise to dramatically change drug therapy is the entire field of nanotechnology, defined as manufactured materials that are <100 nm in one dimension and possess unique physical properties due to this size (NRC, 2006). Applications range from their use as drug carriers to truly futuristic applications including nanofactories, artificial ribosomes or wholly manufactured cells. The unique properties of nanomaterials related to structural stability and quantum-scale reactive properties open up a world of possibilities that could be exploited to target drug delivery or create truly microscale biological sensors. Nanotechnology offers here another challenge to come to this goal a bit closer, to deliver the drug in the right place at the right time. Nanomaterials may be manufactured with tissue targeting biomolecules to reduce the dose required to achieve an efficacious effect. Multifunctional nanoparticles are being considered which contain tumor seeking sensors, imaging agents as well as receptor-triggered release of toxins that could revolutionize the therapy of cancer (Service, 2005).

Nanomaterials may also be constructed out of block-polymers of the drug itself that would allow truly controlled release at the tissue target site. Depending on the particle charge, surface properties, and relative hydrophobicity, nanoparticles can be designed to adsorb preferentially on organs or tissues. The selected transport, or in some cases restricted transport of nanomaterials, may further enhance their ability to be used to target or restrict drug delivery.

3. High-throughput screening

The automation of numerous aspects of modern chemistry and biology allows for biological activity of drugs as well as their adverse effects to be rapidly screened without the need for detailed hypothesis-driven research to be conducted. All aspects of early drug discovery and development are impacted by this increasingly automated science. Combinatorial chemistry allows generation of massive number of study compounds that might be useful for a specific therapeutic target. These libraries of compounds may contain thousands of chemical entities sharing a common chemical motif. High throughput screens can then be used to select compounds with desirable ADME properties or for the highest activity from in vitro tests (e.g. cloned receptor assays, micro-arrays looking for specific therapeutic targets). Additional tests aimed toward assessing toxicological potential are then used to further whittle down candidate drugs. Recently there is a development of an in vitro high-throughput membrane coated fiber array technique using gas chromatography/mass spectrometry (GC/MS) that is predictive of dermal chemical absorption in pigs (Xia et al., 2007). Full development of such approaches would allow rapid identification of drug candidates capable of being delivered by a desired route without the need to conduct *in vivo* trials.

4. Control and targeted drug delivery

Most promising technology to have an effect in next decade is controlled and targeted drug delivery. Near term applications of such strategies include adding polymer groups, such as polyethylene glycol (PEG), to protein and peptide drugs to prolong systemic residence times (Greenwald, 2001). In addition, enhanced SAR knowledge has allowed the selection of drug molecules with inherent longer half-lives that eliminate the needs for short-interval administration. As knowledge of the determinants of nanoparticle cellular uptake mechanisms is gained (Ryman-Rasmussen et al., 2007). Nano based therapeutics targeted to specific cell types will be developed. Electrically-assisted transdermal delivery systems, developed a decade ago and on the market for some human applications, may have direct use in veterinary medicine (Riviere and Heit, 1997). One promise was for delivering of charged or peptide drugs not normally able to penetrate the stratum corneum barrier. Controlled-release transdermal patches and formulations for compounds such as fentanyl used in humans may also be formulated for optimal use in individual species, as our knowledge of species differences in drug absorption expands (Riviere and Papich, 2001). More sophisticated approaches that have been experimentally developed include the use of multicompartment microchips containing multiple doses of a drug, or multiple drugs, that can be released by several mechanisms (Langer, 2001). More advanced technology that is close to being commercially of value are microneedles, structures of such a small diameter that puncturing the skin does not produce any sensation. Such systems would allow construction of drug patches for controlled delivery of substances not normally able to penetrate intact skin (Verbaan et al., 2007). Suggested applications range from delivery of therapeutic proteins to genes, the latter which could be used to transform skin cells to secrete systemically available polypeptide hormones, including growth hormone, transferring, and clotting factors (Khavari et al., 2002). The successful development of such systems would dramatically change the way we treat chronic deficiency diseases in veterinary patients. In addition, such applications might also be well suited to use in food producing animals since chemical residues resulting from traditional dosage forms would not exist. A more direct application that has already shown proof of concept is to coat solid microneedles with antigens for non-invasive vaccine delivery (Wren et al., 2007).

5. Pharmacogenomics

Pharmacogenomics is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single nucleotide polymorphism with a drug's efficacy or toxicity. By doing so, Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype to ensure maximum efficacy with minimal adverse effects. Such approaches promise the advent of "personalized medicine." in which drugs and drug combinations are optimized for each individual's unique genetic makeup. Pharmacogenomics is the whole genome application of pharmacogenetics which examines the single gene interactions with drugs.

As we unlock the genetic code of more species, breeds and microorganisms, we will be better able to more specifically target drugs to species and disease specific endpoints. As more data is collected in more species with defined diseases, we begin to learn the determinants of what are now called idiosyncratic drug effects. The application of statistical algorithms to gene expression data is relatively recent. However, continued development of

these bioinformatics techniques will greatly increase the utility of these data sets. Increased understanding of mechanisms of susceptibility in one species may directly carry over to those of veterinary interest.

Metabolic deficiencies due to lack of an enzyme or drug transporter, as for example the Collie breed sensitivity due to the absence of the MDR-1 gene coding for p-glycoprotein transporter (Mealey, 2004) will be better defined and screened. In the future these could even potentially be incorporated into microfluidic devices. What is lacking is the correlation of specific genes or networks to a biological endpoint. The routine application of pharmacogenomics may also be used to develop oligonucleotide drugs targeted at genetic endpoints (e.g. anti-sense drugs), although this author doubts this will have a major impact on veterinary therapeutics over the next few decades.

The immediate application may be to determine and monitor antimicrobial resistance. Additionally, genomics is already being used to rapidly develop more effective and targeted vaccines for much less cost in shorter times. This has already been having an impact of veterinary medicine.

Genomics, proteomics, and metabonomics are being combined into many approaches to screen for toxicological effects (Riviere, 2006), holding promise to reduce the so-called drop-out rate of lead drug candidates. As we gain experience with interpreting these systems, we will generate increasingly integrated databanks to allow more accurate SAR studies to be conducted. As these relationships are validated, they allow for the development of more robust in silico pharmacology and toxicology screens. What was once called exercises in data-mining is now the field of analytics, with graduate training programs being conducted to train specialists in analyzing such integrated database.

Impact of these trends to veterinary pharmacology

All of the above techniques streamline and optimize the drug discovery process across all therapeutic classes. They thus have a predictable impact on all domains of veterinary medicine through next -decade time span. Novel therapeutic classes of drugs do not belive to replace existing compounds – that is oligonucleotides and exotic material nanodrug devices replacing organically synthesized drugs. Rather there will be a refinement of drugs based on more specific activity with reduced potential for side effects using high-throughput analysis applied to combinatorial chemistry libraries, or alternatively SAR used to design drugs with specific attributes. Components of these increasingly efficient screens will include separate tests for ADME, efficacy, toxicity as well as antimicrobial resistance to ensure that viable drug candidates emerge.

Drugs formulated with specific targeting moieties may be more common. The delivery of drugs will be greatly enhanced and controlled using technologies that are already in the process of being commercialized, for example using advanced polymer chemistries, nanodrug formulations, microneedles, or electrically-assisted delivery techniques. Species-specific drug delivery devices should be more common which make administering drugs to animals easier and less frequent. Cats are the obvious target of many of these approaches.

In food animal pharmacology, microbial resistance will continue to dominate antimicrobial use, although vaccination approaches should reduce the diseases they are used to treat. This would further decrease market share and thus potentially the development of novel compounds. This lack of profitability of antimicrobial drugs is also a crisis facing human medicine. Non-hormonal growth regulating technologies should emerge. Drugs approved in food animal species will have short to non-existent withdrawal times based on better SAR, and drug delivery devices will be less invasive and have minimal impact on carcass quality or safety. Individual animal tracking using implanted microchips may generate the epidemiological databases that would foster management of drug resistance problems. Implantation of biochemical sensors based either on nanotechnology or microfluidics coupled to wireless alert devices might even allow sentinel monitoring of specific genetic markers or metabolites of select bacteria (e.g. enteropathogenic *E. coli* H0157) or chemical exposures to prevent such animals from entering the food supply.

Major challenges

a. Regulatory approval: Although such advancements may be predicted based on trends in a number of different developing technologies, the ultimate ability of products to emerge will be a function of the pathway for regulatory approval of such novel compound and systems. In the past, regulatory agencies have been inelastic in adapting to new technologies; good examples being the difficulty of replacing visual meat inspectors with specific microbial screening tests (NRC, 2001), or batch product testing with real-time individual-unit product manufacturing technologies (e.g. Process Analytical technology [PAT]) (Rantanen, 2007). How will combination products (novel drug in a computer controlled microfluidic device) be tested and approved? Will regulatory agencies allow development to much targeted populations? Will agencies regulate the product or its method of manufacture?

b. Global harmonization: Differences in time to market between regulatory jurisdictions (e.g. United States and European Union) might have major impacts on how these advances are moved into practice. True global harmonization animal drug regulations would remove impediments to rapid drug approval and marketing.

c. Economics: The second major hurdle is the economics of developing such differentiated products for increasingly smaller but more targeted populations of animals. The time to drug development should be reduced from the technological perspective. However, the economics must be favorable for more targeted drugs to be developed for smaller populations of animals. The same holds true for personalized medicine in humans, as the economic model has not yet been developed to allow such niche drug development to replace the need for blockbuster drugs. There must be a value-added benefit to make the investment worthwhile

Conclusions

So where will veterinary therapeutics be in next decade? There will be further but accelerated refinement of our drug armamentarium over the next decade. Therapeutic targets will be greatly increased so that the veterinary pharmacology text or journal 10 years from now (assuming the concept of a hard-copy book survives) may be longer and contain many more drugs tailored to more specific endpoints. Vast improvements in targeted and controlled delivery of existing drugs should improve the ease of administration as well as safety-efficacy profiles. The field will be more diverse and specialized, requiring the pharmacologist to bridge many sub-disciplines. These will indeed be challenging and exciting times!

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