IPORSIP-2000

PLENARY LECTURES
WEDNESDAY, SEPTEMBER 6, 2000

PLENARY LECTURE I.
(PDD)
Iontophoretic Delivery Of Apomorphine: From In Vitro Modelling To The Patient

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Iontophoresis is the enhanced transdermal delivery of popular drugs. Hence, it expands the range of drugs available for transdermal delivery. Iontophoresis may enhance skin drug transport by the factor 1000 in comparison to passive transport with a rapid onset/offset of drug action. Furthermore, drug transport is controllable and programmable with minimal inter and intra-subject variability. Due to its non-availability after oral application apomorphine was chosen as a suitable drug candidate for iontophoretic delivery due to its high potency. Apomorphine is a dopamine agonist and acts directly with the D_2-receptor. A new iontophoretic continuous flow-through transport cell has been developed aiming at a minimal contribution of the cell conformation and experimental protocol to overall transport kinetics of apomorphine. The steady state iontophoretic flux was 90 ± 6 $nmol.cm^2.h^{-1}$ when a 15 mM apomorphine solution was applied in the anodal chamber at a current denisty of 500 $mA.cm^{-2}$. Applied current densities and resulting fluxes were linear in a wide range. In order to study PK/PD relationships in Parkinson patients a stepwise intravenous infusion was given and the pharmacodynamic response was measured using a tapscore. In a first study with patients apomorphine was given iontophoretically for a 1 hr preiod. Simulation of the expected blood levels showed that (sub) tehrapeutic apomorphine levels could be reached. Further increase may be obtained using co-treatment of suitable penetration enhancers. Skin irritation after iontophoretic experiments was mild and reversible. As a further therapeutic strategy (sub) therapeutic basic oral therapy (e.g. with levodopa) may be superimposed by iontophoretic apomorphine therapy for fine-tuning to obtain optimal treatment.

PLENARY LECTURE II.
(PDD)
Perspective Of New Drug Development By Drug Delivery Research

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A concept of new drug development shall be changed. For this, we need a renaissance of thinking. Our discussion of new drug development usually tends to orient toward synthetic drugs.

New drug development can be achieved by finishing products of higher selectivity of drug for medical treatment. There are two ways of approach to get higher selectivity of drug:

a) discovery of new compounds with high selectivity of drug;
b) innovation in drug delivery that is new formulation and/or method with high selectivity of drug by integration and harmonization of various hard/soft technologies.

As the science and technology in the 21st century is said to be formed on:

1) hybrid,
2) high quality
3) husbandry,

the drug development by innovative drug delivery research is exactly based on science and technology of 3Hs. Its characteristic points are interdisciplinary/interfusional, international, of philosophy/ethics and systems of hard/hard/heart. Here, I would emphasize the importance of heart as the products are for human being.

As new drug development by innovative drug delivery researches, several examples of marketed products will also be explained:

A) mucoadhesive drug delivery systems
B) lipid microspheres (Lipo PGE1)
C) Leuprorelin Depot (injection)
D) SMANCS (SMA: poly stylene-co-maleic acid half n-butylate; NCS: neocarcinostatin; in Lipiodol, a lipid contrast medium)
E) TTS tape (Frandol tape; isosorbide dinitrate preparation;
F) Anti-inflammatory cataplasms.

PLENARY LECTURE III.
(PBIO)
Chitosan Nanoparticles As Delivery Systems For High Molecular Weight Immunostimulants

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Immunostimulants have been discovered and isolated in this laboratory from Mycobacteriae, in particular M. Bovis (BCG vaccine) and M. vaccae. These compounds have considerable in vivo antineoplastic activity and have potential for use in the treatment of tubeculosis and cancer as well as vaccine adjuvants. Altohugh orally active, they are difficult to formulate because of their very high molecular weights (up to 25 Mda). We have found a method for preparing nanoparticles of chitosan without the use of solvents and these could be loaded with materials such as bovine serum albumin (BSA) or PS4A, the peptidoglycan isolated from M. vaccae. In vitro dissolution experiments demonstrated that 100% of the BSA was released at modest loadings, but up to 65% of the total dose at high loadings (1000 μg/1.38 mg) was retained and this would only be released by a matrix swelling and erosion mechanism. PS4, which is not charged, was released slowly by what appears to be an initial rapid or burst phase of approximately 40% of the incorporated drug, followed by a controlled diffusional release from the swollen interior of the matrix of the nanoparticles. Implications for the use of these systems for controlled delivery of the immunostimulants in biological environments is discussed.

PLENARY LECTURE IV.
(PBIO)
Formulation Of Microparticles For The Mucosal Delivery Vaccines

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There is an urgent need for pharmaceutically acceptable delivery systems and adjuvants for new and existing vaccines and non-parenteral adiministration for immunological, practical and economic reasons. To this end, biodegradable microparticles show particular promise. Particulate polymeric carriers made from biodegradable synthetic polymers such as polyesters offer advantages in uniformity and flexibility. Earlier studies have demonstrated that microsphere-associated vaccine antigens and plasmid DNA can lead to significant immune responses, not only through parenteral delivery, but also through mucosal surfaces, especially through the nasal route, that the responses induced can be optimized through formulation. These studies illustrated the importance of particle characteristics such as hydrophobicity, size and surface charge, as well as polymer type, molecular weight and crystallinity, on the modulation of immune response obtained. In these studies, the more hydrophobic particles gave higher immune responses than the less hydrophobic ones, positively charged ones better than uncharged ones, higher molecular weight and highly crystalline polymers better than lower molecular weight and less crystalline ones, and smaller particles better than larger ones. In addition, these responses may also be increased by the addition of bioadhesives. Recent publications from our group show the ability of mucosally administered microencapsulated recombinant subunit antigens derived from Y. pestis, to completely protect experimental animals from aerosolised challenge with virulent Plague causing bacteria. For the same microsphere preparation, when delivered intratracheally in a comperative study, which also investigated i.m. and i.n. routes of delivery, mucosal routes (both lung and nasal) gave equivalent or better immune responses than the parenteral route. Botulism toxins are amongst the most lethal substances known to science. We have now demonstrated that it is possible to fabricate microsphere containing a recombinant fusion of maltose binding protein and the 50 kDa carboxy-terminal binding domain of the Botulism toxin F heavy chain (MBP-FHc). SDS PAGE behavior of the microencapsulated protein demonstrated a high degree of commonality with that of native antigen, implying that the microencapsulation process had not resulted in detrimental structural modification. Importantly, two appropriately timed intranasal administrations of microencapsulated MBP-FHc, was seen to engender solid protection following intraperitoneal challenge with more than 10^4 LD50's of pure Botulism toxin F. Again, in the context of clinically relevant antigens, I will also discuss the formulation of microparticulate systems which elicit strong humoral and cellular immunity after only a single mucosal or parenteral administration. We have also shown that, in addition to particle transference into mucosal inductive sites, such as NALT, we observed immunologically significant translocation of microparticulate material into systemic inductive sites, such as spleen. These data will be discussed in the context of mucosal administration of microparticulate vaccine carrier systems.