symposium drug targeting

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Abstracts of papers

PARTICULATE SYSTEMS AS CARRIERS FOR SITE-SPECIFIC DRUG DELIVERY: THE STATE OF THE ART

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In the last decade a number of particulate carrier systems have been developed to change the therapeutic efficacy of drugs after intravenous injection. Among these are nanoparticles, liposomes, gelatin and albumin microspheres. The objectives for designing these systems varied widely: from a sustained action to site specific delivery of the encapsulated drug.
Critical points for the selection of a carrier system are: 1) the ability of the carrier-homing device combination to deliver the drug at the desired sites; 2) the acute and chronic toxicity of these systems and their immunogenicity; 3) the preparation and shelf life of the products.
For homing devices antibodies and certain glycolipids are under investigation. The results indicate that site specific delivery is hampered by the limited ability of the carriers to pass the wall of the blood vessels and the strong affinity of the cells of the reticulo-endothelial system (RES) for these "foreign" bodies. Therefore, target sites should be located either in the compartment of injection (general circulation) or in the cells of the RES.
Distribution kinetics in vivo are susceptible to composition, size and charge of the carrier system. A proper definition of the product is therefore essential to obtain results that are sufficiently reproducible.
In this presentation some of the conclusions mentioned above will be illustrated and discussed in more detail.

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DRUG TARGETING: FACT OR FICTION ? RECEPTOR MEDIATED ENDOCYTOSIS AS A POTENTIAL MECHANISM FOR TISSUE-SPECIFIC DRUG DELIVERY

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An increased drug selectivity can in principle be obtained by covalently linking of drugs to a biodegradable carrier. The particular macromolecule should be specifically recognized by receptors for endocytosis on the cell surface of the organ or tissue where the drug is required for its action. A local drug delivery of potentially very toxic compounds may not only decrease undesirable side effects and toxicity on other tissues ("passive targeting"), but can also produce a marked increase in potency of the drug ("active targeting"). The simplicity of the drug targeting concept however is inversely related to the complexity in the proper design of therapeutic dosage forms for human use. Apart from pharmaceutical problems such as chemical stability, practical routes of administration and costs of manufacturing, chronic toxicity on the RES system as well as possible immunogenicity have to be taken into account. In addition, the intracellular fate of the drug-carrier complex not only in normal but also in heterogenous pathological tissue should be clearly defined before rational claims of improved drug specificity can be made. Examples are hepatotropic carrier-systems for antiviral agents directed to viral hepatitis, antiprotozoal compounds (malaria etc.), antineoplastic agents, enzymes for treatment of genetic enzyme deficiencies, exogenous cholesterol to manipulate cholesterol synthesis, diphteria toxin to inhibit protein synthesis, folinic acid to "rescue" hepatocytes from general toxicity of methotrexate and probes for testing hepatic lysosomal function. Interestingly some of these designs can be extrapolated to other tissues and may well reach the stage of clinical testing. It is concluded that the research of drug targeting requires a multidisciplinary cell biological as well as an integral pharmaceutical approach to guarantee practical solutions to the very complex problems in this area.

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MACROMOLECULAR PRODRUGS OF ADRIAMYCIN

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SUMMARY
The anthracycline antibiotics daunomycin and 14-hydroxydaunomycin (adriamycin, ADR) are very effective in the treatment of a number of malignancies. However, due to cardiotoxic side effects the cumulative dose may not exceed a certain value. We are developing ADR-polymer conjugates (1,2) with the aim of improving the therapeutic index by using the concept of the lysozomotropic prodrug. A plasma-stable polymer-bound drug is internalized by cells by pinocytosis and degraded in the lysozomal compartments by many digestive enzymes at an acidic pH (pH 4-5) releasing the free drug.
We prepared a series of aminoribosyl-bound prodrugs of ADR using poly(α-L-glutamic acid), PGA as a carrier and different peptides as spacers (1,2). The conjugates were studied for their capacity to inhibit the growth of mouse leukemia L1210 and mouse melanoma B16 cells (1,2). The cytotoxic activity of the conjugates increases with increasing length of the spacer, but remains below (1-10%) that of free ADR. Our current studies include the pinocytosis of some of the ADR-polymer conjugates into cells using laser flow cytometry and laser microscopy as well as the release of ADR effected by papain as a representative enzyme for lysozomal enzymes. These studies may allow the optimization of the release of ADR from polymeric prodrugs.

1. W.A.R. van Heeswijk et al. in Recent Advances in Drug Delivery Systems (J.M. Anderson and S.W. Kim, eds.), pp. 77-100, Plenum Publ. Co., New York (1984).
2. C.J.T. Hoes et al., Proceedings of the 26th IUPAC Symposium on Polymers in Medicine and Biology, Prague (1984); to be published in Makromol. Chemie (1985).

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