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Carbohydrates and the pharmaceutical industry

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Abstract - A large number of carbohydrates and carbohydrate- derivatives are used as therapeutics or in diagnostics. Examples are found in important areas such as antibiotics and anticoagulants. In this paper the field will be broadly reviewed and some major, recent advances in the fields of antithrombotic therapeutics and ophtalmic surgery will be high-lighted.

Probably no single factor is more important to the long term success of the pharmaceutical industry than being able to bring truly innovative and beneficial products to the market. In this context it is important to realize that innovation in the commercial sense generally means both new technology and the identification of a real customer need (ref. 1). Here a discussion between industry and basic science in academia is usually fruitful.

The pharmaceutical industry have some clear characteristics such as high R and D expenses (usually ca 15 per cent of sales), high marketing/sales expenses, strong influence of regulatory agencies (e.g. FDA). Also, most new therapeutics are protected by a strong patent network.

Carbohydrates are among the most abundant substances and therefore it should not be unexpected that many have had a considerable importance both as therapeutics and diagnostics. The subject has been reviewed earlier(ref.2).

DISCUSSION

The classical example of a carbohydrate containing drug dates back to 1785 when the effect of digitoxin as a treatment in heart failure was first recorded. This drug has been subject to extensive modification to circumvent its narrow therapeutic index without gaining major success.

Probably the largest individual group of carbohydrate-based therapeutics is the antibiotics. The classical example is that of streptomycin (ref. 3) which started a wave of successful research in aminoglycoside antibiotics eventually giving e.g. the kanamycins (ref. 4), gentamycin (ref. 5), and neomycins (ref. 6). Another important group of carbohydrate-based drugs is the cytostatics including examples as daunorubicin (ref. 7, 8), mithramycin and bleomycin (ref. 9). Although the effects of these substances have revolutionized cancer therapy there are still serious side-effects which, as yet, has not been solved.

Sucralfate, a aluminium complex of persulfated sucrose, constitues a new and interesting principle for treatment of ulcus including, inter alia, mechanical protection of the necrotic mucus and induction of bicarbonate secretion (ref. 10).

Finally, considering low molecular weight carbohydrates the importance of nucleotides such as vidarabine (ref. 11) in treatment of disease of viral etiology should be mentioned.

A few high molecular weight carbohydrates have had a major impact in human medicine. Probably the three most important are dextran,heparin,and hyaluronan.

The original idea of using partially hydrolyzed dextran as a plasma substitute dates back to 1942 when B. Ingelman and A Groenvall studied sugar beet juice (ref.12). Already in 1947 a 6 % solution of a dextran fraction had been approved for clinical use in Sweden. By continued studies and development dextran-based products have kept their position as an important plasma substitute with several interesting additional therapeutic benefits (e.g. antithrombotic activity (ref. 12). Starting from the technology base of dextran some other interesting pharmaceuticals were developed. The most important is probably Debrisan®, a wound-cleansing agent, prepared by cross-linking of dextran. The product acts by absorbing wound exudate in secreting wounds and shortens the healing time (ref. 13).

The clinical effects of heparin in therapeutic and prophylactic treatment of thrombosis have been documented for several decades. Heparin has, however, some well-known and serious side-effects such as risk of bleeding, impairment of the thrombocyte function and influence of the lipolytic activity in the plasma. The opportunities to further develop heparin based pharmaceuticals have been hampered by insufficient basic knowledge on the structure of heparin, its structural-functional relationships and pharmaceutical properties. During the last ten years, however, new understanding has been gained in the abovementioned key-areas (ref. 14) and this has formed a new basis for heparin products. One critical observation was that various factors in the coagulation cascade were influenced differently vis-à-vis the molecular weight of heparin fractions generated by nitrous acid degradation (ref. 15). From this and other observations it was possible to develop a new therapeutic (Fragmin®) based on low molecular weight fractions of heparin which combines good antithrombotic effects with lowered side-effects and simplified routines for administration (ref. 16).

Since the use of artificial implants and devices increases rapidly in modern medicine it is of considerable importance to be able to prepare bio-compatible surfaces. A method based on covalent binding of heparin fragments generated by nitrous acid degradation to a polyethylenimine covered surface has proved to give a particular stable and bio-compatible surface (ref. 17). This has been explored for intra-ocular lenses, oxygenators and other devices.

Hyaluronan displays extraordinary reological properties (ref. 18). In the late 70'ies Balazs and co-workers developed the concept of viscosurgery. This has revolutionized ophtalmic surgery, in particular cataract surgery. Here a high molecular weight noninflammatory fraction of hyaluronan, Healon® , is instilled in the eye by a syringe prior to lens extraction and implantation of the new, intra-ocular lens. Healon® facilitates the eye surgery because it maintains space, protects tissues and make it possible to gently maneuver tissues (ref. 19).

This review has focussed on some classical as well as some newer developments in carbohydrate-based pharmaceuticals. In the future we will certainly see several interesting opportunities in the area of glycoconjugates where advances during the 80'ies have been particulary fast. This basic research opens up solutions in such diverse areas as for example tumour markers for diagnostics, drug targetting and metabolic modulation of drug action.

However, any practically important success will depend on close co-operation between scientists in several areas of basic research (e.g. structural studies, functional studies, synthetic chemistry) and applied goal and customer oriented development.

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