Immunosuppressive drugs. Developments in anti-rejection therapy

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Immunosuppressive therapy has come a long way since the introduction of the conventional azathioprine plus low dose corticosteroid regimens of the 1960s. This book opens with an historical overview of the ‘traditional’ immunosuppressive agents but these are then dismissed and the next series of chapters concentrates on cyclosporin A (CsA) – the introduction of which into organ transplantation improved the survival rates for patients and grafts dramatically. The aim of this book is to present ‘developments in anti-rejection therapy’ and so the swift treatment of the more conventional regimens is perhaps justified, but graft rejection and drug toxicities remain major problems in organ transplantation. The reduction of CsA immunosuppression to alleviate side effects is usually accompanied by the addition of other ‘conventional’ agents, e.g. azathioprine and antilymphocyte antibodies, and methylprednisolone remains the first line choice in the treatment of cellular rejection. Perhaps a little more attention could have been paid to the clinical pharmacology of the corticosteroids and azathioprine. In addition, possibly a mention of the genetic factors which influence active metabolite formation from the latter drug would not go amiss. This criticism over, the book has many good points.

Four chapters are devoted to an up-to-date review of the molecular action of CsA, its pharmacokinetics, immunosuppressive properties and clinical efficacy. Importantly, the methodological problems associated with the measurement of CsA, which influence derived pharmacokinetic parameters, are discussed. Because there is a need for more refined pharmacological control of the immune system several new immunosuppressive drugs are currently undergoing clinical trials. A number of chapters are devoted to FK506 (Tacrolimus), a potent and novel immuno-suppressive agent discovered in Japan within the last decade. This section starts with an excellent chapter on the pharmacokinetics and monitoring of this compound which, like CsA, is extensively metabolised by hepatic cytochrome P450IIIA4. FK506 has a narrow therapeutic index and it produces a myriad of metabolites with undefined but potentially biological roles. The chapter on FK506 and experimental organ transplantation also serves as a good review of the model systems available and how they have been utilised in the past. This is followed by a comprehensive, well referenced chapter, on the use of FK506 in clinical transplantation.

There is an excellent chapter on mycophenolic acid, a well known compound to those biochemical pharmacologists with an interest in purine metabolism, which has now donned a new suit of clothes as a potential immunosuppressive agent. Like the ‘historical’ agent azathioprine mycophenolic acid inhibits de novo purine synthesis but, unlike the thiopurine drugs, it does not have the ‘undesirable’ cytotoxic properties i.e. the ability to inhibit DNA and produce chromosome breaks. Mycophenolic acid has shown some success in the treatment of severe rheumatoid arthritis and an early clinical application of the drug is anticipated. Other ‘new’ immunosuppressive agents discussed include mizoribine, brequinor sodium, deoxypergualin, lefunomide and SK&F 105685 in addition to rapamycin, a macroclide antibiotic which inhibits the immune reactions that have escaped the effects of CsA.

In conclusion, this book is firmly targeted at the immunopharmacologist but it contains much information that the clinical pharmacologist, particularly one with a grounding in drug metabolism, would find of interest if they were tempted into the field of immunosuppressive therapy.

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