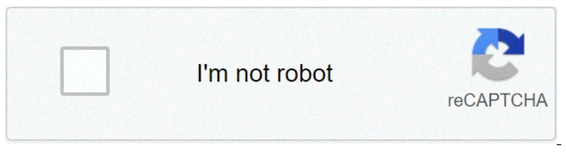

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Clinical pharmacology and therapeutics lecture notes pdf

Presents an up-to-date review of drug use across all major clinical disciplines Offers a timely overview of clinical drug trials and development Provides new clinical scenarios to relate chapter content to real-life application Contains colour-coded "Key Points" and "Prescribing Points" to highlight important information Includes chapter introductions and summaries, and numerous figures, tables, and colour illustrations Lecture Notes Clinical Pharmacology and Therapeutics, Tenth Edition, is an essential resource for medical students, junior doctors, and other prescribers looking for an up-to-date reference on pharmacological principles, prescribing, and therapeutics.Gerard A. McKay is Consultant Physician, Glasgow Royal Infirmary, Honorary Clinical Associate Professor, University of Glasgow, and Visiting Professor, University of Strathclyde, UK.Matthew R. Walters is Head of the School of Medicine, Dentistry & Nursing and Professor of Clinical Pharmacology, University of Glasgow, UK.Neil D. Ritchie is Honorary Senior Lecturer, School of Medicine, Dentistry & Nursing, University of Glasgow, UK. Clinical Pharmacology and Therapeutics 9th editionPrinciples of drug action(pharmacodynamics) Pharmacological agents are used in therapeutics to: 1 Alleviate symptoms, for example: • Paracetamol for pain • GTN spray for angina 2 Improve prognosis – this can be measured in number of diff erent ways – usually measured as a reduction in morbidity or mortality, for example: • Prevent or delay end stage consequences of disease, e.g. anti-hypertensive medication and statins in cardiovascular disease, levodopa in Parkinson's disease • Replace defi ciencies, e.g. levothyroxine in hypothyroid • Cure disease, e.g. antibiotics, chemotherapy 2013 • 330 Pages • 15.47 MB • English Posted April 14, 2020 • Uploaded by hamill.cristopher Report Page 1 CLINICAL PHARMACOLOGY AND THERAPEUTICS Lecture Notes Gerard A. McKay Matthew R. Walters 9th Edition LN with extended material online' Page 3 Clinical Pharmacology and Therapeutics Lecture Notes Page 5 Clinical Pharmacology and Therapeutics Lecture Notes Edited by Gerard A. McKay BSc (Hons) FRCP Consultant Physician and Honorary Clinical Associate Professor Glasgow Royal Inf rmary and University of Glasgow Matthew R. Walters MD FRCP MSc Professor of Clinical Pharmacology Director, Clinical Pharmacology and Therapeutics Institute of Cardiovascular and Medical Sciences University of Glasgow Ninth Edition A John Wiley & Sons, Ltd., Publication Page 6 T is edition f rst published 2013 © 2013 by John Wiley & Sons, Ltd. Previous editions 1982, 1985, 1989, 1992, 1996, 2001, 2006, 2010 Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientif c, Technical and Medical business with Blackwell Publishing. 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Walters, Matthew R. III. Title: Clinical pharmacology and therapeutics. [DNLM: 1. Pharmacological Phenomena. 2. Drug T erapy. 3. Pharmacology, Clinical. QV 37] 615'.1—dc23 2012044843 A catalogue record for this book is available from the British Library. Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books. Cover image: Jan Mika/iStock Cover design by Grounded Design Set in 8.5/11pt Utopia Std by Aptara Inc., New Delhi, India ® 1 2013 Page 7 Contents Contributors, vi 14 Drugs and the urological system, 178 Preface, vii 15 Cancer therapeutics, 185 Foreword, ix 16 Drugs and inf ammatory joint disease, 197 17 Immunopharmacology, 204 18 Drugs and the blood including anticoagulants and thrombolytic drugs, 215 Part 1 Principles of clinical 19 Drugs used for pain relief and anaesthesia, 228 pharmacology 1 Pharmacodynamics and pharmacokinetics, 3 2 Clinical trials and drug development, 11 Part 3 Practical aspects of prescribing 20 Clinical pharmacokinetics: dosage individualisation, 241 Part 2 Aspects of therapeutics 21 Inf uence of renal and hepatic disease on 3 Drugs and gastrointestinal disease, 19 pharmacokinetics and pharmacodynamics, 247 4 Management of coronary artery disease and its 22 Prescribing for the young and the elderly, 252 complications, 29 23 Drugs in pregnant and breastfeeding 5 Primary and secondary prevention of cardiovascular women, 255 disease, 52 24 Pharmacoeconomics: the economic evaluation of 6 Drugs used to treat respiratory disease, 71 new drugs, 262 7 Drugs used to treat neurological disease, 81 25 Poisoning and drug overdose, 269 8 Treatment of psychiatric disorders, 97 26 Drugs you may need in a hurry, 283 9 Antimicrobial therapy, 111 27 Prescribing and its pitfalls, 287 10 HIV and antiretroviral treatment, 132 11 Travel medicine and tropical disease, 143 Self assessment questions, 294 12 Drugs and endocrine disease, 153 Self assessment answers, 299 13 Drugs and the reproductive system, 169 Index, 302 Page 8 Contributors T e following have contributed substantially to the Claire Higgins School of Medicine, University of writing, revision and rewriting of the chapters for this Glasgow ninth edition. Chapter 13, Drugs and the reproductive system Peter Higgins Institute of Cardiovascular and Medi- Prabhakar Rajan Institute of Cancer Sciences, cal Sciences, University of Glasgow University of Glasgow Chapter 1, Pharmacodynamics and pharmacoki- Chapter 14, Drugs and the urological system netics Charles Gourlay University of Edinburgh Jesse Dawson Institute of Cardiovascular and Medi- Chapter 15, Cancer therapeutics cal Sciences, University of Glasgow Islay Morrison NHS Greater Glasgow and Clyde Chapter 2, Clinical trials and drug development Chapter 16, Drugs and inf ammatory joint disease Beth Reed NHS Greater Glasgow and Clyde Jagtar Nijjar Institute of Infection, Inf ammation Chapter 3, Drugs and gastrointestinal disease and Immunity, University of Glasgow Shona Jenkins NHS Greater Glasgow and Clyde Chapter 17, Immunopharmacology Chapter 4, Management of coronary artery disease Nick Heaney Beatson Oncology Centre, Glasgow and its complications Chapter 18, Drugs and the blood including antico- Chapter 5, Primary and secondary prevention of agulants and thrombolytic drugs cardiovascular disease Rachel Harrison NHS Greater Glasgow and Clyde Manish Patel NHS Lanarkshire Chapter 19, Drugs used for pain relief and Chapter 6, Drugs used to treat respiratory disease anaesthesia Edward Newman Institute of Neuroscience and Psy- Kathleen Collins NHS Greater Glasgow and Clyde chology, University of Glasgow Chapter 22, Prescribing for the young and the elderly Chapter 7, Drugs used to treat neurological disease Shazya Huda NHS Greater Glasgow and Clyde Tom McPhee NHS Greater Glasgow and Clyde Chapter 23, Drugs in pregnant and breastfeeding Chapter 8, Treatment of psychiatric disorders women Andrew Seaton Brownlee Centre, Gartnavel General Ailsa Brown Scottish Medicines Consortium Hospital, Glasgow Chapter 24, Pharmacoeconomics Chapter 9, Antimicrobial therapy Kenneth Paterson Scottish Medicines Consortium Nick Kennedy NHS Lanarkshire Chapter 24, Pharmacoeconomics: the economic Chapter 10, HIV and antiretroviral treatment evaluation of new drugs Alisdair MacConnachie Brownlee Centre, Gartnavel Iain Keith NHS Greater Glasgow and Clyde General Hospital, Glasgow Chapter 26, Drugs you may need in a hurry Chapter 11, Travel medicine and tropical disease David Carty Institute of Cardiovascular and Medical Sciences, University of Glasgow Chapter 12, Drugs and endocrine disease Page 9 Preface T e ability to use drugs safely and ef ectively is a phasise the principles of clinical pharmacology, and def ning characteristic of a good doctor. T is ability topics which are of particular clinical importance. is predicated upon an up-to-date knowledge of the Recognition of the importance of prescribing skills ever-expanding pharmacopeia available to modern has prompted a focus on their assessment in UK clinicians. In recent years the advent of translational medical schools. Key prescribing points are empha- and stratif ed approaches to the development of new sised in each chapter, and a series of questions cover- medicines has accelerated the pace of change and re- ing commonly examined topics is included to allow sulted in a profusion of new knowledge across a wide self-assessment. range of therapeutic areas. T is is the f rst edition of Clinical Pharmacology T e extensive changes made to the text of this the and T erapeutics Lecture Notes to have been prepared ninth edition of Clinical Pharmacology and T era- without Professor John Reid, former Regius Professor peutics Lecture Notes ref ect the enormous progress of Medicine and T erapeutics at the University of made in recent years. T e new edition has been Glasgow. John's immense contribution to Clinical extensively revised and updated with signif cantly Pharmacology extends far beyond his founding role expanded sections covering areas which are devel- and expert ste wardship of this textbook over decades. oping rapidly such as immunopharmacology and Both of the current Editors gratefully acknowledge his cancer therapeutics. A particular emphasis has been expert mentorship and guidance which continues to placed upon practical aspects and clinical relevance inf uence the preparation of this text. We hope that throughout each chapter. Although the content of the ninth edition will continue to succeed in the pro- the text has been revised and refreshed, the objec- vision of a clear understanding not only of how but tive of this book remains as set out in the preface to also when to use drugs. its f rst edition more than 30 years ago: to provide a brief, clearly written and up-to-date review of clinical Gerry McKay pharmacology. As in earlier editions we have not at- Matthew Walters tempted to be comprehensive, but have tried to em- Glasgow 著者 : J.L.Reid, P.C.Rubin & M.R.Walters 出版社 : WILEY-BLACKWELL ISBN : 978-1-4051-3519-1 ページ数 : 304pp. 出版年 : 2006年 在庫 定価3,058円(本体2,780円 ＋ 税) You're Reading a Free Preview Pages 16 to 21 are not shown in this preview. You're Reading a Free Preview Pages 31 to 78 are not shown in this preview. You're Reading a Free Preview Pages 88 to 111 are not shown in this preview. You're Reading a Free Preview Page 121 is not shown in this preview. 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Copyright Dr Garry KJ Pettet 2005 - 2009 www.garrypettet.com 4. Preface I wrote these notes as a final year medical student in the UK as I found it very difficult to find a good single text to use for my CPT revision. I used the following textbooks in writing these notes: - British National Formulary (BNF 47 March 2004) - Clinical medicine 5th edition (Kumar, Clark) - Hands-on-guide to clinical pharmacology (Chatu, Milson & Tofield) - Medical pharmacology at a glance 4th edition (Neal) - Oxford handbook of clinical medicine 6th edition (Longmore, Wilkinson & Rajagopalan) - Pharmacology 4th edition (Rang, Dale, Ritter) I have made sure that everything that has been mentioned in our lectures is in these notes. We must thank the following lecturers, as some of their material may well be in these notes: - Dr Chris Bench - Dr Neil Chapman - Dr Anton Emmanuel - Dr Michael Feher - Dr Alun Hughes - Prof Sebastian Johnston - Prof John MacDermot - Dr Janice Main - Dr Vias Markides - Dr Jamil Mayet - Dr Andrew Rice - Dr Stephen Robinson - Dr Mike Schachter - Dr Tom Sensky - Prof Peter Sever - Dr Colin Tench - Dr Simon Thom - Dr Roxaneh Zamegar I would also like to thank Dr Wajid Hussain for proofreading the section on anti-arrhythmics. Although every effort has been made to ensure the accuracy of these notes, I take no responsibility for errors within (but please let me know as I have to revise from these as well!). Dr Garry Pettet Copyright Dr Garry KJ Pettet 2005 - 2009 1 www.garrypettet.com 5. Drug development Surrogate markers: • A biological measurement which substitutes for the therapeutic end-point • Examples: o BP and stroke o Cholesterol and coronary disease • Characteristics of a "good" surrogate: o Biological feasibility o Dose-related response to intervention o Easy to measure o Reproducible o Specific / sensitive o High predictive value o Acceptable by experts / regulatory authorities Types of clinical trials: • Open: o Subject and researcher know what they are getting • Single-blind: o The subjects do not know what they are getting • Double-blind: o No one knows what they are getting (during the trial) • PROBE: o Prospective o Randomised o Open-labelled o Blinded o End-point o This is used for large, complex studies with several treatments. It is an open trial where those who analyse the results do not know who got what treatment The phases of a clinical trial: • Phase 1: o Healthy volunteers (not for cancer / HIV trials) o Few subjects (< 50) o Looks at pharmacokinetics / pharmacodynamic activity / safety • Phase 2: o Patients with the target disease o More subjects (100 – 200) o Usually single-blind trials o Looks again at pharmacokinetics / safety (note, these may be different than in healthy volunteers) • Phase 3: o Patients o Much larger (> 1000) Copyright Dr Garry KJ Pettet 2005 - 2009 2 www.garrypettet.com 6. o Usually double-blind or PROBE o May be parallel or crossover o Multi-centre o May use either "hard" (e.g. MI) or "surrogate" end-points • Phase 4: o Post-marketing o Surveillance for: Adverse drug reactions Rare side-effects Drug interactions Parallel vs crossover studies: • Parallel study: o Most randomised controlled trials (RCTs) are parallel • Crossover study: o Need fewer subjects o Should normally be used in chronic stable diseases and the interventions should have a rapid onset and short duration o Beware of order effects: Carry-over effects Period effects: • Changes in the patient's disease over time Power: • Is the study large enough to answer the study's question? • Type 1 error (α): o Chance of finding 2 treatments are different when they are not o Usually: $\alpha = 0.05$ (i.e. $p < 0.05$) • Type 2 error (β): o Chance of finding 2 treatments are equal when they are not o Usually: $\beta = 0.1$ or 0.2 (arbitrary) • Power = 1 - β (i.e. 80 – 90% usually) • The higher we set β (i.e. the greater our power) the more expensive the trial becomes as we need more subjects Copyright Dr Garry KJ Pettet 2005 - 2009 3 www.garrypettet.com A B A B 7. "Intention to treat" vs "per protocol" analysis: • Intention to treat: o Ignore whether the subjects actually take the medication (i.e. just assume they did) • Per protocol: o Only analyse data from subjects who actually took the medication Copyright Dr Garry KJ Pettet 2005 - 2009 4 www.garrypettet.com 8. Adverse drug reactions Significance: • 3 – 40% of inpatient admissions • Affects 10 – 20% of hospital patients • 4th most common cause of death in US hospital patients • Up to 30 – 60% are preventable Types of adverse drug reaction (ADR): • Type 1: o "Predictable" reactions o Common o Dose-related o A consequence of the known pharmacology of the drug • Type 2: o "Idiosyncratic" reactions o Rare o Usually not dose-related o Allergies o Pharmacogenetic variations Classification of ADRs: • Augmented pharmacological effect • Bizarre • Chronic • Delayed • End-of-treatment Determinants of ADRs: • Drug: o Pharmacodynamics o Pharmacokinetics o Dose o Formulation o Route of administration • Patient: o Age o Co-morbidity o Organ dysfunction o Genetic predisposition • Environment: o Mistakes Allergies vs psuedoallergies: • Allergies: o Type I (anaphylaxis): Copyright Dr Garry KJ Pettet 2005 - 2009 5 www.garrypettet.com 9. Penicillins Contrast media (anaphylactoid) o Type II (cytotoxic antibodies – blood dyscrasias): Haemolytic anaemia: • Methyldopa • Penicillin • Sulphonamides Agranulocytosis: • Carbimazole • Clozapine Thrombocytopenia: • Quinidine • Heparin o Type III (immune complex formation): Penicillin Sulphonamides o Type IV (cell mediated): Topical antibiotics • Pseudoallergies: o Looks like an allergy but is not immune-mediated o Examples: Aspirin - bronchospasm ACE inhibitors – cough Long-term ADRs: • Withdrawal: o Opiates o Benzodiazepines o Corticosteroids • Rebound: o Clonidine o β-blockers • Adaptive: o Neuroleptics Copyright Dr Garry KJ Pettet 2005 - 2009 6 www.garrypettet.com 10. Drug interactions Liver enzyme inducers (cytochrome P450): • Carbamazepine • Phenobarbitone • Phenytoin • Rifampicin Liver enzyme inhibitors (cytochrome P450): • Cimetidine • Ciprofloxacin • Grapefruit juice • Macrolide antibiotics: o Erythromycin • Omeprazole Important drugs metabolised by the liver (cytochrome P450): • Carbamazepine • Cyclosporin A • Combined oral contraceptive (COC) pill • Phenytoin • Theophylline • Warfarin Some important drugs interacting with warfarin: • Drugs increasing the effect of warfarin: o Alcohol o Amiodarone o Antibiotics (many – reduced vitamin K absorption) o Cimetidine o Omeprazole o Simvastatin • Drugs decreasing the effect of warfarin: o Carbamazepine o COC pill o Rifampicin Interactions with diuretics: • General: o Potentiate: ACE inhibitors Lithium o Metabolic: Hypokalaemia enhances digoxin efficacy β-blockers potentiate hypokalaemic effects of diuretics • Loop: o Increased risk of ototoxicity with the aminoglycosides • Potassium-sparing: Copyright Dr Garry KJ Pettet 2005 - 2009 7 www.garrypettet.com 11. o Risk of hyperkalaemia with ACE inhibitors Drugs affecting gastric emptying and hence drug absorption: • Increase emptying: o Metoclopramide • Decrease emptying: o Atropine Impairment of drug excretion: • Probenicid: o Competes with Penicillins for renal tubular excretion, leads to increased concentration of penicillins (can be beneficial) Copyright Dr Garry KJ Pettet 2005 - 2009 8 www.garrypettet.com 12. Pharmacodynamics/pharmacokinetics Half-life (t1/2): • The time taken for the concentration of drug in plasma (or blood) to fall to half it's original value • Drugs with a short t1/2 may have a long duration of action: o So-called "cell-trapping" o E.g. omeprazole Volume of distribution (Vd): • This is the apparent volume into which the drug is distributed Vd = dose / (initial apparent plasma concentration) • Is used to calculate the clearance of a drug • Is high for lipid-soluble drugs • Is low for water-soluble drugs • Values of Vd: o < 5L drug retained within the vascular system o < 15L drug is restricted to the extracellular fluid (ECF) o > 15L indicates the drug is distributed throughout the total body water Clearance: • The volume of plasma (or blood) cleared of drug per unit time • Depends on drug lipid solubility • Clearance (but not t1/2) provides an indication of the ability of the liver and kidneys to dispose of the drug First vs zero order kinetics: • First-order kinetics: o A metabolic process that depends on the drug concentration at any given time is called a first-order process o I.e. a non-saturable process • Zero-order kinetics: o If any enzyme system responsible for drug metabolism becomes saturated, then the rate of elimination proceeds at a constant rate and is unaffected by an increase in the concentration of the drug o I.e. a saturable process o Examples include: Phenytoin Ethanol o The importance of zero-order kinetics is that you could double the dose, but the plasma concentration would not double (may increase to an enormous extent) Bioavailability: • The proportion of administered drug reaching the systemic circulation • IV drugs have 100% bioavailability Copyright Dr Garry KJ Pettet 2005 - 2009 9 www.garrypettet.com 13. • Drugs with high bioavailability: o Ciprofloxacin (near 100%) • Drugs with low bioavailability: o Bisphosphonates (~15%) First-pass metabolism: • Also known as pre-systemic metabolism • This is drug metabolism that occurs before the drug reaches the system circulation • Occurs in the liver and gut wall • Some drugs undergo extensive first-pass metabolism: o Levodopa o Lignocaine o Morphine o Nitrates (e.g. GTN) o Propranolol o Verapamil • Is generally a nuisance for two reasons: o A larger dose is needed when it is given orally o Marked individual variations occur Post-systemic metabolism: • The main purpose is to increase water-solubility of the drug • Phase I: o Three types of reaction: Oxidation: • Most important are the P450 enzymes • Xanthine oxidase metabolises 6-mercaptopurine • Monoamine oxidase inactivates 5-HT, NA, tyramine Reduction / Hydrolysis o Usually produces a more reactive compound that will be acted on by phase II components o May activate a prodrug – examples: Levodopa dopamine Enalapril enalaprilat Azathioprine 6-mercaptopurine Methyldopa α-methyl-noradrenaline Carbimazole methimazole • Phase II: o Conjugation of a drug or phase I metabolite with an endogenous substance to form a more polar, easily excreted, compound o May be either: Glucuronidation Sulphation Acetylation (does not alter water-solubility) Copyright Dr Garry KJ Pettet 2005 - 2009 10 www.garrypettet.com 14. Glutathione Loading doses: • In practice, a steady state concentration is effectively achieved after three plasma half-times • Faster attainment of the steady state is achieved by starting with a larger dose – a loading dose Therapeutic drug monitoring: • Why? o To investigate lack of drug efficacy o Possible poor compliance o Suspected toxicity o Prevention of toxicity • Type of drugs: o Narrow therapeutic index (TI) o Uncertain dose / concentration relationship o Defined plasma concentrations with no active metabolites • Examples: o Not warfarin (this measures the INR, not drug concentration!) o Antibiotics (aminoglycosides, vancomycin) o Anticonvulsants (carbamazepine, phenytoin) o Aminophylline / theophylline o Cyclosporin A o Digoxin o Lithium Copyright Dr Garry KJ Pettet 2005 - 2009 11 www.garrypettet.com 15. Prescribing in renal / liver disease Important drugs whose elimination is affected by renal impairment • Half-lives are approximate ranges when renal impairment present • Amoxicillin (t1/2 2 – 14 hours): o Applies to most penicillins o Toxic effects: Seizures (especially in meningitis) Rashes are more common in renal impairment • Atenolol (t1/2 6 – 100 hours): o Contraindicated in: Asthmatics Severe heart failure Peripheral vascular disease o Toxic effects: Bradycardia Confusion Hypotension • Captopril (t1/2 2 – 14 hours): o Toxic effects: ⇓ GFR Angioedema Cough: • Probably due to a direct effect on sensory afferents • Not bradykinin GI disturbances Hypotension Taste disturbances • Digoxin (t1/2 36 – 90 hours): o Requires therapeutic drug monitoring (TDM) o Toxic effects: Dysrhythmias (VT, heart block) Gynaecomastia Nausea (severe) / vomiting Xanthopsia (distortion of yellow colour vision) • Gentamicin (t1/2 2½ - >50 hours): o Increased risk of toxicity when: Dehydrated (important as septic patients usually are) Hyponatraemic o Toxic effects: Nephrotoxicity (renal tubular damage) Ototoxicity (can be irreversible) Vitamin D and the kidney: • Vitamin D has to undergo two hydroxylation reactions within the body to become active Copyright Dr Garry KJ Pettet 2005 - 2009 12 www.garrypettet.com 16. • Kidney forms the 1-hydroxy form of vitamin D and requires the enzyme 1α-hydroxylase • In renal impairment, the above step may not happen • Bone disease caused by renal disease is termed renal osteodystrophy: o Loss of vitamin D activity o ⇑ PTH activity • Replacing vitamin D: o Alfacalcidol (the 1-hydroxylated form, thus negating need for 1α-hydroxylase) o Calcitriol (the active 1, 25-hydroxylated form) – rarely used Nephrotoxic drugs: • ACE inhibitors: o ⇓ GFR (if the arterial perfusion pressure is low): Renal artery stenosis (especially bilaterally) Coarctation of the aorta • Cyclosporin A: o Used in renal transplants o Is a substrate for P450 (levels may be increased by other drugs) o ⇓ GFR o Damages tubular function • Gentamicin: o Renal tubular damage • Lithium: o Nephrogenic diabetes insipidus o Renal tubular damage • NSAIDs: o ⇓ GFR o Papillary necrosis: Loss of PG-mediated vasodilatation o Na^+ retention • Others: o Urate stones: Anticancer drugs (tumour lysis syndrome) o Myoglobinuria: Alcohol Statins Drugs to watch when patient has impaired hepatic synthetic function: • Hypoalbuminaemia: o Drugs which bind to albumin and are cleared by the liver: Diazepam Phenytoin Tolbutamide • A1-acidic glycoprotein deficiency: o Binds basic drugs: Chlorpromazine Imipramine Copyright Dr Garry KJ Pettet 2005 - 2009 13 www.garrypettet.com 17. Quinidine • Reduced synthesis of clotting factors: o Warfarin: If the liver is synthesising even less of factors II, VII, IX and X then warfarin's effects will be potentiated o Antibiotics: Interfere with vitamin K production in the gut by bacteria May compound the above problem Drugs to watch in a patient with current / recent hepatic encephalopathy: • Antidepressants: o Tricyclic antidepressants (TCAs) are safest (but use a ⇓ dose) o Avoid monoamine oxidase inhibitors (MAOIs): Idiosyncratic hepatotoxicity • Anti-psychotics: o Chlorpromazine • Anxiolytics / hypnotics: o Oxazepam / temazepam are the safest o Avoid chlormethiazole (especially IV) • Opiates: o Can precipitate coma o Even low levels are dangerous Drugs with a high first-pass metabolism: • These drugs will not be metabolised as much in liver impairment (if given orally), thus the dose should be ⇓ • Chlorpromazine • Chlormethiazole • Imipramine • Morphine / pethidine • Propranolol • Verapamil Hepatotoxic drugs: • Cholestasis: o Chlorpromazine (reversible cholestasis) o Sulphonylureas (e.g. glibenclamide) o Carbimazole • Hepatocellular necrosis: o Antibiotics: Isoniazid Rifampicin Nitrofurantoin o Anticonvulsants: Can cause liver damage at normal doses in some patients Carbamazepine Phenytoin Valproate Copyright Dr Garry KJ Pettet 2005 - 2009 14 www.garrypettet.com 18. o Anti-hypertensives: Hydralazine: • Also causes a SLE-like syndrome (ssDNA Abs) Methyldopa o Halothane (repeated exposures) o Paracetamol (overdose) Copyright Dr Garry KJ Pettet 2005 - 2009 15 www.garrypettet.com 19. Rheumatology Drug treatment of osteoarthritis (OA): • Simple analgesics: o Paracetamol (as good as Ibuprofen in early disease) • Topical therapy: o NSAIDs (e.g. ibuleve) o Capsaicin: Potent pain-producing agent After a few applications, the pain-producing effect disappears and nociceptive responses to other stimuli disappear as well – hence it's use here • Glucosamine • Systemic NSAIDs Drug treatment of rheumatoid arthritis (RA): • NSAIDs • COX-II inhibitors: o Indications: Age >65 years Previous history of DU / GU or GI bleed Large doses of NSAID required to control pain o Absolute contraindications: Established IHD Cerebrovascular disease Heart failure (NYHA II – IV) • Gastroprotection (if on NSAID / long-term steroids): o H2-receptor antagonists o Proton pump inhibitors (PPIs) o Misoprostol • Disease modifying anti-rheumatic drug (DMARD): o Persisting synovitis >6 weeks o Several may have to be tried to find the right one: Methotrexate Sulphasalazine Gold Penicillamine Hydroxychloroquine • Anti-TNFα therapy: o Progressive RA after 2 DMARD failures • Steroids are controversial but useful in acute flares Drug treatment of osteoporosis: • Bisphosphonates: o Are the mainstay of treatment • Calcium supplements • Vitamin D • Calcitonin (may be considered) • HRT no longer has role Copyright Dr Garry KJ Pettet 2005 - 2009 16 www.garrypettet.com 20. Glucosamine: • Unclear mechanism of action • Probably similar efficacy to simple NSAIDs • Better tolerated than NSAIDs but not free of side-effects: o Headache o Rash o Drowsiness Non-steroidal anti-inflammatory drugs (NSAIDs): • (Non- selectively) inhibit cyclo-oxygenase (COX) • COX converts arachidonic acid (derived from membrane phospholipids) into endoperoxides • The endoperoxides are further converted into: o Prostaglandins (PGs): Potentiate the activity of other pain mediators Vasodilatation o Thromboxane A2: Platelet aggregation Vasoconstriction o Prostacyclin: Inhibits platelet aggregation Vasodilatation • There are 2 isoforms of COX - COX-I and COX-II: o COX-I is a constitutional enzyme and is important in the maintenance of the protective GI mucus barrier in the stomach and of renal blood flow o COX-II is expressed at sites of inflammation • NSAIDs are: o Analgesic o Antipyretic (inhibits the rise in brain PGs that cause pyrexia) o Anti-inflammatory (at higher doses) • Adverse effects: o GI: Peptic ulceration (major adverse effect) o Renal: Reduced renal blood flow Sodium retention - hypertension Interstitial nephritis Hyperkalaemia Papillary necrosis (chronic use) o Other: Bronchospasm (especially in asthmatics) Allergies Aspirin as a NSAID: • Aspirin is a NSAID but the large doses required to control the inflammation in the arthritides led to an unacceptable number of adverse effects Copyright Dr Garry KJ Pettet 2005 - 2009 17 www.garrypettet.com 21. • It irreversibly inactivates COX – activity returns only when new enzyme is synthesised: o Hence it's effectiveness in platelets (cannot synthesise new enzyme) Paracetamol as a NSAID: • Like aspirin, paracetamol is a NSAID • It's mechanism of action is not fully understood and it has no anti- inflammatory activity • It works, act least partly, by reducing COX tone: o This activity is only seen in areas of low peroxide concentration o Hence, paracetamol works best when there is little or no leucocyte infiltration (as leucocytes produce high levels of peroxide) Relative risk of GI toxicity with NSAIDs: • From least toxic to most toxic: o Ibuprofen o Diclofenac o Aspirin o Naproxen o Indomethacin o Ketoprofen COX-II inhibitors: • E.g. Celecoxib (Rofecoxib (Vioxx) has been withdrawn in the UK)) • No better at improving symptoms of pain / inflammation than NSAIDs • 50% reduction in GI: o Ulceration o Perforation o Bleeds • (Probable) increased risk of: o Myocardial infarction o Stroke Methotrexate: • Indications: o Malignancy o Psoriasis (when conventional therapy fails) o Rheumatoid arthritis Copyright Dr Garry KJ Pettet 2005 - 2009 18 www.garrypettet.com 22. • Mechanism of action: o Inhibits dihydrofolate reductase o Leads to a reduction in the production of tetrahydrofolic acid (which is essential for nucleic acid synthesis) o Prevents cells from dividing • Administer concurrent folic acid to minimise symptoms • Adverse effects: o Nausea o Fatigue o Pneumonitis (rare but can be life-threatening) • Contraindications: o Renal / hepatic impairment o Pregnancy • Interactions: o NSAIDs / probenicid: Reduce the excretion of methotrexate Sulphasalazine: • Mechanism of action in RA is unknown • Adverse effects: o Nausea / abdominal discomfort o Reduced sperm count o Marrow suppression • Contraindications: o Salicylate allergy o Renal impairment Gold: • Adverse effects: o Marrow suppression o Proteinuria o Hepatitis Penicillamine: • Adverse effects: o Marrow suppression o Proteinuria o Reduction in taste o SLE • Contraindications: o Penicillin allergy o SLE Hydroxychloroquine: • Adverse effects: o Rash o Retinopathy (rare) o Tinnitus • Cautions: Copyright Dr Garry KJ Pettet 2005 - 2009 19 www.garrypettet.com 23. o Hepatic impairment • Very toxic in overdose Anti-TNFα therapy: • TNFα is the major mediator of inflammation • Used in RA when patient has failed to respond to >=2 DMARDs (including methotrexate) • Can be either: o Soluble TNFα receptors (etanercept) o Anti-TNFα receptors (infliximab) • Reduce inflammation, inhibit progression and improve radiological Sharp score (a measure of radiological RA severity) • Adverse effects: o Local reactions o Increased risk of infections: Especially tuberculosis (need to screen before therapy) o Demyelination syndromes o SLE-like syndrome: Avoid in SLE-sufferers o Worsening of pre-existing heart failure • Other disease indications: o Ankylosing spondylitis o Psoriatic arthritis o Crohn's disease Bisphosphonates: • E.g. alendronate, pamidronate • Are enzyme-resistant analogues of pyrophosphate • Bind to hydroxyapatite crystals and reduce bone resorption (via inhibition of osteoclasts) • Indications: o Osteoporosis (both primary and steroid-induced) o Paget's disease o Malignant hypercalcaemia • Adverse effects: o Alendronate can cause oesophagitis: Swallow the tablet whole with a full glass of water on an empty stomach and remain upright for at least 30 mins Vitamin D supplementation: • Usually given as ergocalciferol (vitamin D2 – the usual dietary source of vitamin D) • Is a fat-soluble vitamin so bile salts are necessary for absorption • Adverse effects: o Hypercalcaemia • Interactions: Copyright Dr Garry KJ Pettet 2005 - 2009 20 www.garrypettet.com 24. o Some anticonvulsants (carbamazepine, phenytoin) increase the requirement of vitamin D Copyright Dr Garry KJ Pettet 2005 - 2009 21 www.garrypettet.com 25. Gastroenterology Drug treatment of GORD / PUD: • Antacids • Acid suppression: o H2-receptor antagonists o Proton pump inhibitors (PPIs) • Helicobacter pylori eradication Drug treatment of constipation (laxatives): • Bulk laxatives • Stimulant laxatives • Osmotic agents • Stool softeners • Suppositories / enemas • Novel: o Motilin analogues (e.g. erythromycin) o 5-HT4 antagonists (e.g. tegaserod) o Probiotics Drug treatment of diarrhoea: • General: o Opioids (e.g. loperamide) • Autonomic neuropathy (e.g. diabetes): o Clonidine o Octreotide (for secretory diarrhoea) • Bacterial overgrowth: o Treat underlying cause o Cyclical antibiotics if above fails (e.g. neuropathy) • Pancreatic insufficiency (e.g. diabetes, chronic pancreatitis): o Pancreatin + acid-suppressant (e.g. PPI) Drug treatment of Crohn's disease: • Acute exacerbations: o Steroids (oral / rectal / IV) o Elemental diet o Anti-TNFα therapy (infliximab): Severe (especially fistulating) disease • Maintenance: o 5-Aminosalicylic acid (5-ASA) compounds o Azathioprine (if 5-ASA fails) o Methotrexate (if azathioprine intolerant) Drug treatment of ulcerative colitis: • Acute exacerbations: Copyright Dr Garry KJ Pettet 2005 - 2009 22 www.garrypettet.com 26. o Rectal 5-ASA (evidence shows benefit over steroids) o Steroids (oral / rectal / IV) • Maintenance: o 5-ASA compounds Antacids: • Increase gastric pH (this increases rate of emptying thus action is short) • All antacids can interfere with drug absorption – should be taken separately • Sodium bicarbonate: o Only useful water-soluble antacid o May cause metabolic alkalosis • Magnesium hydroxide: o May cause diarrhoea • Aluminium hydroxide: o May cause constipation • Alginate-containing compounds (e.g. Gaviscon): o Form a "raft" on top of stomach contents and prevent reflux H2-receptor antagonists: • E.g. ranitidine, cimetidine • Block histamine receptors on the gastric parietal cell membrane and reduce acid secretion • Indications: o GORD o PUD • Adverse effects (mainly cimetidine): o Liver enzyme inhibitor (increases levels of): Anticonvulsants (carbamazepine, phenytoin, valproate) Theophylline Warfarin o Hyperprolactinaemia o Anti-androgenic activity (gynaecomastia) Proton pump inhibitors (PPIs): • E.g. omeprazole, lansoprazole • Inactive at neutral pH but are activated in the stomach and irreversibly inhibit the H^+/K^+-ATPase (proton pump) • Are more effective than H2-receptor antagonists and more cost- effective • Indications: o GORD o PUD o Zollinger-Ellison syndrome • Adverse effects: o Liver enzyme inhibitor (increases levels of): Copyright Dr Garry KJ Pettet 2005 - 2009 23 www.garrypettet.com 27. Phenytoin Warfarin • Cautions: o Achlorhydria is associated with gastric cancer – unsure of long- term effects of acid suppression H. pylori eradication therapy: • One PPI and two antibiotics for two weeks • Usual combination (but there are many): o Omeprazole o Clarithromycin o Amoxicillin (or metronidazole) • Resistance to metronidazole is common Bulk laxatives: • E.g. bran, ispaghula • Only good for mild constipation • Are usually indigestible polysaccharides • Increase the volume of the intestinal contents – thus stimulating peristalsis by stretching mechanoreceptors • Gradual onset of action (~1 week) • Increase stool output as a function of initial stool weight: o If stool volume is low initially then won't see much of an increase • Adverse effects: o Exacerbates bloating in slow-transit constipations Stimulant laxatives: • E.g. bisacodyl, picosulphate, senna • Are inactive glycosides that are activated in the colon by bacteria • Once in colon – have direct stimulant effect on the myenteric plexus: o Smooth muscle contraction (peristalsis) • Also increase secretion of water and electrolytes • Rapid onset of action (~8 hours) – give in evening for morning stool • Adverse effects: o Colic o Colonic atony o Hypokalaemia o Pseudomelanosis coli (colonic pigmentation with chronic use) o Unpredictable effect Osmotic agents: • E.g. Lactulose, magnesium salts • Poorly absorbed solutes that maintain a large stool volume by osmosis • Lactulose: o Is a disaccharide (fructose-galactose) o Cannot be cleaved by human disaccharidases – is cleaved by bacteria in the colon Copyright Dr Garry KJ Pettet 2005 - 2009 24 www.garrypettet.com 28. o These sugars are poorly absorbed by the colon and act as osmotic laxatives • Onset of action: o Salts – hours o Lactulose – 2 or 3 days • Adverse effects: o Cramps o Flatulence o Hypermagnesaemia (especially in renal impairment) with Mg salts Stool softeners: • E.g. sodium docusate, arachis oil • Act like detergents in the colon and facilitate mixing of fat and water in the stool • Adverse effects: o Passive faecal leakage • Not effective enough to be used on their own Suppositories / enemas: • E.g. glycerine suppositories, phosphate enemas • Probably as effective as oral osmotic laxatives Opioids and diarrhoea: • E.g. loperamide, codeine, morphine • Stimulate μ-receptors on myenteric neurones and lead to hyperpolarization: o Inhibits Ach release from myenteric plexus and reduces peristalsis • Loperamide is most appropriate as it does not cross the blood-brain barrier and is unlikely to cause dependence Pancreatin: • Pancreatic enzyme supplement of porcine origin • Must be taken with an anti-acid drug (usually a H2-receptor antagonist) to prevent it's destruction in the stomach • Is inactivated by heat – caution if mixing pancreatin in with food • Indications: o Cystic fibrosis o Chronic pancreatitis o Diabetes mellitus o Pancreatectomy • Adverse effects: o Nausea / vomiting o Abdominal discomfort o Irritation of buccal / perianal mucosa 5-Aminosalicyclic acid (5-ASA) compounds: • E.g. mesalazine, olsalazine, sulphasalazine Copyright Dr Garry KJ Pettet 2005 - 2009 25 www.garrypettet.com 29. • Unknown mechanism of action • Indications: o Induction of remission in UC (rectal preparation) o Maintenance of remission in UC and CD: 1 year relapse rate (73% placebo vs 21% sulphasalazine) • Probably reduce the cancer risk associated with UC • Drug structures: o Olsalazine: Two 5-ASA molecules joined by an azo bond that is cleaved by bacteria in the colon o Sulphasalazine: 5-ASA with sulphapyridine (a sulphonamide) The sulphapyridine carries the 5-ASA to the colon Most of the adverse effects are caused by sulphapyridine • Adverse effects: o Few with the newer agents (lacking sulphapyridine) Infliximab: • An anti-TNFα monoclonal antibody • Indications: o Crohn's disease not controlled by steroids and a conventional immunosuppressant o Refractory fistulating Crohn's disease • 65% of patients initially respond to infliximab • 30% will go on to remission • Of those that respond to a single treatment – 50% maintain remission when treated for 1 year • Infliximab closes 50% of refractory fistulas within 2 weeks and improves healing in 65%: o However, only 30% of those who heal remain healed at 1 year • Adverse effects: o Local reactions o Increased risk of infections: Especially tuberculosis (need to screen before therapy) o Demyelination syndromes o SLE-like syndrome: Avoid in SLE-sufferers o Worsening of pre-existing heart failure Copyright Dr Garry KJ Pettet 2005 - 2009 26 www.garrypettet.com 30. Antivirals Treatment of herpes simplex virus (HSV) and varicella zoster virus (VZV): • Aciclovir (topical / oral / IV) • Second-line: o Famciclovir (good for genital herpes) o Valaciclovir Treatment of cytomegalovirus (CMV): • Ganciclovir (IV) (can cause myelosuppression) • Second-line: o Valaciclovir o Foscarnet Treatment of human immunodeficiency virus (HIV): • Highly active anti-retroviral therapy (HAART): o Two NRTIs plus either an NNRTI or a PI • NRTI = nucleoside reverse transcriptase inhibitor • NNRTI = non- nucleoside reverse transcriptase inhibitor • PI = protease inhibitor • Treatment of opportunistic infections Drugs treatment of chronic hepatitis B (HBV) infection: • 40% success rate • Interferon-α (IFN-α) given as a subcutaneous injection • Lamivudine • Second-line: o Famciclovir Drug treatment of chronic hepatitis C (HCV) infection: • Combination therapy (most effective, up to 60% 'cured'): o Peginterferon-α (⇑ bioavailability – once weekly) o Ribavirin • Treatment depends on HCV genotype: o Genotypes 2, 3: Better prognosis Treat for 6 months o Genotypes 1, 4: Worse prognosis Treat for 12 months • If HCV RNA has not decreased after 12 weeks treatment to 25/min • Pulse >110/min • PEFR α) • "Cardio-selective" (β1-antagonists): o Atenolol o Metoprolol • Indications: o Angina o Heart failure o Hypertension o Post-MI o Prevention of variceal bleeding in liver disease (propranolol) o Prophylaxis of migraine o "Stress"-induced arrhythmias • Mechanism of action: o Most do not affect resting parameters (e.g. heart rate) but prevent the exercise-induced cardiovascular changes caused by sympathetic stimulation o Anti-hypertensive action probably arises from an alteration in the CNS "set-point" • Adverse effects: o Lethargy / fatigue (usually improves with use) o Bradycardia o Cold hands / feet o Hypotension o Bronchospasm (including cardio-selective agents) o Nightmares o Worsened / precipitated heart failure • Contraindications: o Asthma / COPD o Bradycardia / heart block • Interactions: o Diltiazem / verapamil: ⇑ risk of bradycardia / AV block o Insulin / oral anti-diabetic agents: β-blockers mask the signs of hypoglycaemia Calcium-channel blockers: • Two classes: o Dihydropyridines: Nifedipine (short-acting) Amlodipine (longer-acting) o Non-dihydropyridines: Diltiazem Verapamil • Indications: o All: Angina (especially vasospastic angina) Copyright Dr Garry KJ Pettet 2005 - 2009 41 www.garrypettet.com 45. Hypertension o Nifedipine: Raynaud's phenomenon o Verapamil: Supraventricular arrhythmias: • Adenosine has largely replaced in acute situation • Can be used as prophylaxis against SVTs • Mechanism of action: o Block L-type voltage-sensitive Ca^{2+} channels in: Arterial smooth muscle (vasodilatation): • Both classes • Can cause a reflex tachycardia Myocardial conduction system (negative inotropism): • Non-dihydropyridines (as they have a high affinity for channels in the activated state • Amlodipine causes less tachycardia than nifedipine • Verapamil (and to a lesser extent diltiazem) depress the sinus node: o Mild resting bradycardia • Verapamil slows conduction at the AVN • Diltiazem has actions in between verapamil and nifedipine: o Popular in treatment of angina – does not cause tachycardia • Adverse effects: o Fluid retention (ankle oedema): Can be severe enough to merit withdrawal Is a local effect that has nothing to do with Na^+ retention o Headaches o Hypotension o Flushing o Gum hypertrophy • Contraindications: o All: Cardiogenic shock o Dihydropyridines: Severe aortic stenosis / HOCM Unstable angina o Non-dihydropyridines: Myocardial conduction defects (e.g. bradycardia) Heart failure: • Further depression of cardiac function o Nifedipine: Angina (short-acting preparation may ⇑ mortality) o Verapamil: Ventricular tachycardia (potentially lethal) AF with Wolff-Parkinson-White syndrome • Interactions: o Diltiazem: Digoxin: • Diltiazem ⇑ plasma concentration of digoxin Copyright Dr Garry KJ Pettet 2005 - 2009 42 www.garrypettet.com 46. Carbamazepine: • Diltiazem ⇑ plasma concentration of carbamazepine Phenytoin: • Diltiazem ⇑ plasma concentration of phenytoin o Nifedipine: Diltiazem: • ⇑ plasma levels of nifedipine Phenytoin: • Nifedipine ⇑ plasma levels of phenytoin Grapefruit juice: • ⇑ plasma levels of nifedipine (and other dihydropyridines but not Amlodipine) o Verapamil: β-blockers (asystole, severe hypotension, heart failure) Digoxin: • Verapamil ⇑ plasma concentration of digoxin Cyclosporin: • Verapamil ⇑ plasma concentration of cyclosporin Angiotensin converting enzyme inhibitors (ACEIs): • E.g. captopril, enalapril, lisinopril • Indications: o Diabetic nephropathy o Hypertension o Heart failure o Post-MI • Inhibit ACE, thus reduce circulating angiotensin II • Actions of angiotensin II (mediated via the AT1 receptor): o Potent vasoconstrictor o Aldosterone secretion: Na^+ retention K^+ excretion • Advantages: o Do not affect blood lipids o May improve cardiac remodelling • Adverse effects: o Postural hypotension: Usually first-dose More common in sodium-depleted patients o Dry cough (Chinese are more susceptible) o Hyperkalaemia o Angioedema (in 1 – 2% of patients) • Contraindications: o Poor renal arterial perfusion pressure: Renal artery stenosis / coarctation of the aorta: • Loss of renal efferent arteriole tone (caused by the ACEI) and ⇓ afferent arteriole pressure leads to renal ischaemia Copyright Dr Garry KJ Pettet 2005 - 2009 43 www.garrypettet.com 47. o Aortic stenosis o Pregnancy • Interactions: o NSAIDs: ⇑ risk of renal impairment o Potassium-sparing diuretics: ⇑ risk of hyperkalaemia o Lithium: ACEIs ⇓ excretion of lithium o Diuretics: ⇑ risk of hypotension Angiotensin II (AII) receptor antagonists: • E.g. losartan, irbesartan, candesartan • Indications: o Diabetic nephropathy o Hypertension o Heart failure (unlicensed indication) • Mechanism of action: o Block the AT1 receptor, inhibiting the actions of angiotensin II o As they do not block ACE, they do not affect the metabolism of bradykinin – possibly why they do not cause a cough • Adverse effects/contraindications/interactions – as for ACE inhibitors Digoxin: • Indications: o Supraventricular dysrhythmias (esp. AF) for ventricular rate control o Heart failure (improves symptoms not mortality) • Mechanism of action: o Is a cardiac glycoside extracted from foxglove leaves o Inhibits cardiac membrane Na^+/K^+-ATPase: ⇑ intracellular Na^+ Secondary ⇑ in intracellular Ca^{2+} • Clinical effects: o ⇑ force of cardiac contraction o ⇑ cardiac vagal activity: ⇓ heart rate ⇓ AV conductance ⇑ AVN refractory period • Common adverse effects: o Anorexia o Nausea o Vomiting • Toxic levels: o Digoxin requires therapeutic drug monitoring o Risk of toxicity increased with: Hypokalaemia (reduced competition for pump binding) Hypercalcaemia Copyright Dr Garry KJ Pettet 2005 - 2009 44 www.garrypettet.com 48. Hypothyroidism o May require digoxin specific antibody fragments (Fab) o Features: Nausea (severe) Dysrhythmias: • VT • Heart block Xanthopsia (distortion of yellow colour vision) • Contraindications: o Complete heart block o HOCM o Wolff-Parkinson-White syndrome • Caution in renal impairment: Digoxin is excreted by the kidneys • Drugs increasing risk of digoxin toxicity: o Anti-arrhythmics: Amiodarone Quinidine o Calcium channel blockers (non-dihydropyridines)): Diltiazem Verapamil o Diuretics (loop and thiazide): Cause hypokalaemia, thus ⇑ risk of digoxin toxicity Nicorandil: • Indications: o Angina • Mechanism of action: o Potassium channel activator with a nitrate component o Causes both arterial and venous vasodilatation • Adverse effects: o Headache o Flushing o Oral ulceration (rarely) • Interactions: o Sildenafil: Profound hypotension – avoid concomitant use Copyright Dr Garry KJ Pettet 2005 - 2009 45 www.garrypettet.com 49. Endocrinology Drug treatment of hyperthyroidism: • Immediate symptom control: o Propranolol • Long-term treatment: o Thionamides: Carbimazole or Propylthiouracil o Radioiodine (131 I) • Prior to surgery to decrease thyroid vascularity: o Lugol's iodine solution Immediate management of thyrotoxic storm: • IV fluids • Take blood for T3, T4 (and cultures if infection suspected) • Sedate if necessary: o E.g. chlorpromazine • Propranolol (oral or IV if no contraindications) • Digoxin: o May be needed to slow the heart • Anti-thyroid drugs: o Carbimazole o Lugol's solution • Corticosteroids (IV hydrocortisone or oral dexamethasone) Drug treatment of hypothyroidism: • Hypothyroidism: o Levothyroxine (T4) • Myxoedema coma: o Liothyronine (T3) Drug treatment of Addison's: • Disease: o Oral hydrocortisone: 20mg in the morning 10mg in the evening Double during febrile illness, stress or injury o Fludrocortisone: Only needed if: • Postural hypotension • ⇓ Na^+, ⇑K^+ or ⇑ renin Give every second day • Crisis: o Hydrocortisone 100mg IV stat o IV fluids (colloid to resuscitate then crystalloids) o Glucose IV if hypoglycaemic o Antibiotics if infection present Copyright Dr Garry KJ Pettet 2005 - 2009 46 www.garrypettet.com 50. Drug treatment of Cushing's syndrome: • Treat the underlying cause – rarely need drug therapy long-term • Suppression of plasma cortisol level: o Aminoglutethimide o Ketoconazole o Metyrapone Drug treatment of Conn's syndrome: • Definitive treatment is with surgery • Spironolactone Drug treatment of diabetes insipidus (DI): • Cranial DI: o Treat the underlying cause o Intranasal desmopressin (DDAVP) • Nephrogenic DI: o Treat the underlying cause o Bendrofluazide (paradoxically, as this is a diuretic) Drug treatment of acromegaly: • Best treated with trans-sphenoidal surgery or irradiation • Somatostatin analogues (first line): o Octreotide (short-acting) o Lanreotide (long-acting) • Dopamine agonists: o Bromocriptine o Cabergoline Drug treatment of hypopituitarism: • Need to replace what is missing • ACTH: o Hydrocortisone • GH: o Recombinant GH is available • FSH, LH: o Testosterone - males o Oestrogen (via COC pill) - females • TSH: o Thyroxine (if hypothyroid, but can't use to TSH to monitor) • No need to replace prolactin Drug treatment of hypogonadism: • Males: o Testosterone Copyright Dr Garry KJ Pettet 2005 - 2009 47 www.garrypettet.com 51. • Females: o COC pill Drug treatment of hyperprolactinaemia: • Definitive treatment is surgical • Dopamine agonists: o Bromocriptine o Cabergoline Drug treatment of hypercalcaemia: • Treat underlying cause if possible • IV fluids • Bisphosphonates • Salmon calcitonin: o Rarely used o Faster onset than bisphosphonates • Steroids: o E.g. for sarcoidosis • Furosemide (once rehydrated) Drug treatment of hypocalcaemia: • Mild: o Oral calcium supplements (e.g. sandocal) • Severe: o 10mls 10% calcium gluconate IVI over 30 mins o Repeat as necessary • Must correct magnesium levels – will never correct Ca^{2+} otherwise Drug treatment of phaeochromocytoma crisis: • Control BP with IV phentolamine (short-acting α-antagonist) • When BP controlled, give phenoxybenzamine (irreversible α- antagonist) • Give β1-blocker • Arrange for surgery within next few weeks Thionamides: • E.g. carbimazole, propylthiouracil • Indications: o Carbimazole: Hyperthyroidism o Propylthiouracil: Usually reserved for patients intolerant to carbimazole • Mechanism of action: o All: Inhibition of thyroid peroxidase Immunosuppressive properties (controversial) Copyright Dr Garry KJ Pettet 2005 - 2009 48 www.garrypettet.com 52. o Carbimazole: Is a prodrug (converted to methimazole) o Propylthiouracil: Inhibits peripheral conversion of T4 T3 • How to use: o Aim is to render the patient euthyroid and then give a ⇓ dose for maintenance o It is often possible to stop treatment after 1 or 2 years (50% relapse rate) • Adverse effects: o GI disturbances o Carbimazole: Pruritis Rash o Agranulocytosis: Carbimazole (0.1%) Propylthiouracil (0.4%) Patients should be told to seek medical attention if they develop symptoms of infection (e.g. sore throat): • If neutropenia confirmed stop treatment • Cautions: o Pregnancy: Low doses should be used as carbimazole crosses the placenta and can cause neonatal hypothyroidism / goitre PTU is less problematic in pregnancy Radioiodine (131 I): • Treatment of choice in pts >40 years (can be used in younger pts) • Indications: o Hyperthyroidism o Disseminated thyroid malignancy • Mechanism of action: o The radioactive iodine is localised to the thyroid where it destroys thyroid tissue via β-radiation • Treatment renders the pt euthyroid within 4-6 weeks, when thyroxine replacement therapy can be undertaken (lifelong) • Adverse effects: o Causes hypothyroidism o May precipitate thyroid storm • Contraindications: o Children o Pregnancy (also, pregnancy must not be allowed to occur within 3 months) o Mothers who are unable to leave their children in others care for at least 10 days (to avoid exposure) Thyroxine: • May be either T4 (Levothyroxine) or T3 (liothyronine) • T3 is faster acting than T4 but with a shorter half-life Copyright Dr Garry KJ Pettet 2005 - 2009 49 www.garrypettet.com 53. • Adverse effects (mainly in overdose): o Angina o Dysrhythmias (including AF) o MI o Tachycardia o Hyperthyroid symptoms (even when TSH in normal range) • Cautions: o Thyroxine should be introduced slowly in those with IHD • Interactions: o Warfarin: Thyroxine ⇑ the effect of warfarin Corticosteroids: • E.g. hydrocortisone, prednisolone, dexamethasone • Indications (many): o Anti-inflammatory: Topical: • Asthma • Skin disorders (e.g. eczema) Systemic: • Anaphylaxis • IBD • Rheumatoid arthritis o Immunosuppression: Connective tissue diseases (e.g. temporal arteritis) Leukaemia Sarcoidosis Transplant rejection o Replacement: Addison's disease Congenital adrenal hyperplasia • Mechanism of action: o Bind to cytoplasmic receptor that diffuses into nucleus and binds to steroid-response elements on DNA: Either increases or decreases transcription with numerous effects o Inhibits phospholipase A2 (thus ⇓ production of arachidonic acid) o ⇓ B and T cell responses to antigens • Adverse effects (many): o CNS: Depression Psychosis o Endocrine: Adrenal suppression Hirsuitism Copyright Dr Garry KJ Pettet 2005 - 2009 50 www.garrypettet.com 54. Impotence Oligo-/amenorrhoea Weight gain o Eyes: Cataracts Glaucoma o Gastrointestinal: Candidiasis Peptic ulceration Pancreatitis o Immune system: ⇑ susceptibility to and ⇑ severity of infections o Metabolic: Hyperglycaemia Hypertension o Musculoskeletal: Growth suppression Myopathy Osteoporosis o Skin: Abdominal striae Buffalo hump Easy bruising Poor wound healing Thinning • Differences between the different steroids: o Hydrocortisone: Replacement therapy IV in shock / status asthmaticus o Prednisolone: Orally for anti-inflammatory effects o Dexamethasone: No salt-retaining properties Very potent Useful when high doses required (e.g. cerebral oedema) o Budesonide / beclomethasone: Pass membranes very poorly Much more active topically (e.g. aerosol, gut) • Interactions: o Enhances activity of warfarin o Live vaccines (impairs response) o Reduces activity of anticonvulsants (carbamazepine, phenytoin) • Withdrawal of glucocorticoids – withdrawal gradually in the following: o Course duration >3 weeks o Received >40mg prednisolone (or equivalent) daily o Been given repeated doses in the evening o Taken a short course within 1 year of taking long-term therapy • Notes: Copyright Dr Garry KJ Pettet 2005 - 2009 51 www.garrypettet.com 55. o "Physiological" dose of steroid is ~7.5mg prednisolone o Patients should be given a steroid card Metyrapone: • Indications: o Cushing's syndrome: Especially that not amenable to surgery (e.g. lung ca) o Resistant oedema due to aldosterone secretion in: Cirrhosis Congestive cardiac failure • Mechanism of action: o Competitive inhibitor of 11β-hydroxylase o Inhibits endogenous production of cortisol (and to a lesser extent aldosterone) by the adrenals • Contraindications: o Adrenocortical insufficiency o Pregnancy / breast feeding • Adverse effects: o Hypoadrenalism Desmopressin (DDAVP): • Synthetic vasopressin (ADH) analogue • Indications: o Cranial diabetes insipidus (diagnosis and treatment) o Haemophilia o Persistent enuresis • Mechanism of action: o Selectively agonises V2 receptors on renal tubular cells: Leads to increased reabsorption of water Thus devoid of vasoconstrictor activity (V1) o Also increases the plasma concentration of factor VIII • Adverse effects: o Dilutional hyponatraemia o Fluid retention • Contraindications: o Heart failure Somatostatin analogues: • E.g. octreotide (given tds), lanreotide (given once monthly) • Indications: o Acromegaly o Carcinoid syndrome o Variceal bleeding (octreotide, unlicensed indication) • Mechanism of action in acromegaly: o Inhibits GH release from the pituitary gland o 90% of patients respond and 60% have GH level normalisation Copyright Dr Garry KJ Pettet 2005 - 2009 52 www.garrypettet.com 56. • Adverse effects: o Gallstones o GI disturbances • Interactions: o Anti-diabetic agents (oral and insulin): Octreotide may ⇓ requirements for these drugs Dopamine agonists: • E.g. bromocriptine (short-acting), cabergoline (long-acting) • Indications: o Acromegaly o Hyperprolactinaemia o Idiopathic Parkinson's disease o Suppression of lactation o Cyclical benign breast disease • Mechanism of action: o Directly stimulate dopamine receptors in the CNS (anti- Parkinson's effect) o Inhibits release of prolactin from anterior pituitary o Inhibits the release of GH in acromegalics: Increases GH levels in non-acromegalics • Lead to a maximum ⇓ of GH of 7-60%: o Only 10-15% of patients achieve GH normalisation • Adverse effects: o Nausea / vomiting o Postural hypotension o Drowsiness / confusion o Dyskinesia o Fibrotic reactions (rare): Pericardial / pulmonary and retroperitoneal fibrosis • Domperidone (D2 antagonist): o Can be used to relieve the peripheral adverse effects of bromocriptine (does not cross the BBB so has no effect on CNS effects) • Interactions: o Erythromycin and sympathomimetics (e.g. dobutamine): Increase the plasma concentration of bromocriptine Growth hormone: • E.g. somatrophin • Indications: o Adults: GH deficiency o Children: GH deficiency Chronic renal impairment Turner's syndrome Testosterone: Copyright Dr Garry KJ Pettet 2005 - 2009 53 www.garrypettet.com 57. • E.g. restandol (oral), sustanon (IM), andropatch (transdermal patch) • Indications: o Male androgen deficiency • Adverse effects: o Androgenic effects: Fusion of epiphyses in prepubertal boys (stunted growth) Hirsuitism Male pattern baldness Acne o Prostate abnormalities (enlargement ± malignancy) o Cholestatic jaundice • Contraindications: o Cancers: Male breast Primary liver tumour Prostate • Interactions: o Warfarin: Potentiates actions of warfarin Combined oral contraceptive (COC) pill: • E.g. cilest, microgynon • Are preparations containing both an oestrogen and a progestogen • Indications: o Contraception o Menstrual cycle control / menorrhagia o Mild endometriosis o Premenstrual symptoms • Mechanism of action: o Exerts a negative feedback on the pituitary and inhibits gonadotrophin release, and thus inhibits ovulation • Adverse effects: o Major: ⇑ risk of venous thromboembolism (VTE) ⇑ risk of hypertension ⇑ risk of breast carcinoma (small) o Minor: Breast tenderness Headaches Nausea Weight gain • Contraindications: o Absolute: History of CVA / IHD / VTE Migraine (severe / focal) Blood clotting disorders Active breast / endometrial cancer o Relative: Copyright Dr Garry KJ Pettet 2005 - 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Age > 40 years Obesity Smokers • Interactions: o Drugs reducing the efficacy of the COC pill: Broad-spectrum antibiotics P450 inducers: • Carbamazepine • Phenytoin • Rifampicin o Warfarin: Oestrogens (including the COC pill) reduce the effect of warfarin • The COC pill should be stopped several weeks prior to an elective surgical procedure to ⇓ risk of VTE Calcitonin: • E.g. calcitonin (porcine natural), salcatonin (synthetic salmon calcitonin) • Indications: o Hypercalcaemia (rarely) o Malignant bone pain o Osteoporosis o Paget's disease of bone (especially pain relief) • Mechanism of action: o Lowers serum calcium: Inhibits osteoclast activity Increases renal Ca^{2+} excretion • Adverse effects: o Facial flushing o Nausea / vomiting o Tingling sensation in the hands o Unpleasant taste in the mouth α1-antagonists: • Non-selective (α1 and α2): o Phentolamine (short-acting) o Phenoxybenzamine (irreversible, long-acting) • α1: o Prazosin o Doxazosin o Tamsulosin (Flomax) • Indications: o Non-selective α-blockers: Phaeochromocytoma o α1-blockers: Copyright Dr Garry KJ Pettet 2005 - 2009 55 www.garrypettet.com 59. Hypertension Benign Prostatic hypertrophy (doxazosin, tamsulosin) • Mechanism of action: o Antagonism of post-synaptic α1-adrenoceptors leads to vasodilatation o α1 blockade also leads to relaxation of the internal urethral sphincter, resulting in ⇑ urinary flow • Adverse effects: o First-dose hypotension • Interactions: o Other hypotensive agents - ⇑ risk of hypotension Copyright Dr Garry KJ Pettet 2005 - 2009 56 www.garrypettet.com 60. Lipids Which patients require lipid-lowering therapy? • Primary prevention: o Guidelines are frequently changing Total [chol] >5mmol/L and CHD risk >30% over 10yrs or 10yr CHD risk >=15% • Secondary prevention: o History of CVS event (angina, MI, PVD, CVA) ± o [chol] >=5mmol/L • Choice of drug: o First choice therapy: Statin o Second choice therapy: Fibrates Anion exchange resins • Note about diet: o Diet lowers [cholesterol] only by ~10% (as we endogenously synthesise cholesterol, not just eat it) Drugs used to treat obesity: • Orlistat • Sibutramine Statins: • E.g. simvastatin, atorvastatin, pravastatin • Usually taken at night • Reduce incidence of all cardiovascular events and total mortality • Mechanism of action: o Are HMG-CoA reductase inhibitors – block the rate-limiting step in hepatic cholesterol synthesis o Due to the ⇓ concentration of cholesterol in the hepatocytes, there is an ⇑ in the number of hepatic LDL receptors o This leads to a ⇓ in plasma LDL o Those with homozygous familial hypercholesterolaemia do not respond to statins (as they have no LDL receptors) • Adverse effects (all uncommon): o Myositis: o Patients complain of weakness / aching muscles If CK >5x upper limit of normal discontinue Can lead to rhabdomyolysis and renal failure If this occurs, cannot use a statin again o Altered LFTs • Contraindications: o Liver disease o Pregnancy • Interactions: o Drugs increasing the risk of myositis: Copyright Dr Garry KJ Pettet 2005 - 2009 57 www.garrypettet.com 61. Cyclosporin Fibrates o Warfarin: Statins potentiate the actions of warfarin • Patients should have their LFTs monitored regularly whilst on a statin Fibrates: • E.g. bezafibrate, gemfibrozil • Actions: o Unclear mechanism – possibly stimulate lipoprotein lipase o ⇓ TGs (~30%) o ⇓ LDL (~10%) o ⇑ HDL (10%) • Are first line drugs in patients with hypertriglyceridaemia (who are at risk of pancreatitis and retinal vein thrombosis) • Adverse effects: o GI disturbance o Myositis o Gallstones • Contraindications: o Hepatic / renal impairment o Pregnancy • Interactions: o Statins: ⇑ risk of myositis o Warfarin: Potentiate the actions of warfarin Anion exchange resins: • E.g. cholestyramine, cholestipol • Mechanism of action: o Bind bile acids in the bowel o Forces the liver to synthesise more bile acids – causes an increase in the expression of LDL receptors and lowering of LDL • Adverse effects: o GI disturbance: Bloating Constipation Nausea / vomiting o May aggravate hypertriglyceridaemia o Impairs the absorption of many drugs o May impair the absorption of fat soluble vitamins: May require supplements of vitamins A, D and K Omega-3-oils (fish oils): • Can be effective in hypertriglyceridaemia • Adverse effects: Copyright Dr Garry KJ Pettet 2005 - 2009 58 www.garrypettet.com 62. o Fish-like odour to the patient Orlistat: • Indications: o Adjunct in obesity management: BMI >30 if no diabetes BMI >27 if diabetic • Mechanism of action: o Pancreatic lipase inhibitor o Impairs absorption of dietary fat • Adverse effects: o GI disturbance: Probably why the drug works as patients reduce their fat intake to reduce the side-effects o May impair the absorption of fat soluble vitamins: May require supplements of vitamins A, D and K • Contraindications: o Cholestasis o Pregnancy • Interactions: o Warfarin: Difficulty in controlling the INR Sibutramine: • Indications: o As for orlistat • Mechanism of action: o Centrally acting anorectic o Inhibits reuptake of noradrenaline and 5-HT • Adverse effects: o Hypertension o Many others • Contraindications: o Many, mainly cardiovascular Copyright Dr Garry KJ Pettet 2005 - 2009 59 www.garrypettet.com 63. Clotting Antiplatelet drugs: • Aspirin • Dypyridamole • Clopidogrel • GP IIb/IIIa receptor antagonists: o Abciximab Anticoagulants: • Oral: o Warfarin • Parenteral: o Unfractionated heparin o Low molecular weight heparin (LMWH) Thrombolytic agents: • Streptokinase • Tissue plasminogen activator (tPA) Indications for antiplatelet drugs: • Acute coronary syndromes • Primary prevention of cardiovascular events: o If 10yr CVD risk >=20% (with a controlled blood pressure) • Secondary prevention of cardiovascular events: o CVA / TIA o IHD o PVD • Heart valve replacements • AF (in those who cannot be anti-coagulated) Indications for oral anti-coagulants: • AF • Prophylaxis / treatment of VTE: o DVT o PE • Mechanical heart valve replacements • Dilated cardiomyopathy / left ventricular aneurysm • ? TIAs Indications for parenteral anti-coagulants: • Acute coronary syndromes • Acute arterial obstruction • Treatment of VTE: o DVT o PE Indications for thrombolytic agents: • Acute myocardial infarction Copyright Dr Garry KJ Pettet 2005 - 2009 60 www.garrypettet.com 64. • Arterial thrombus • Life-threatening PE • Occluded lines / shunts Aspirin: • Indications: o Mild to moderate pain o Pyrexia o Anti-platelet: Acute myocardial infarction History of: • Angina • Intermittent claudication • Myocardial infarction • Stroke • TIA AF (in patients where warfarin is contraindicated) Kawasaki syndrome (only childhood indication) • Mechanism of action: o Irreversibly inactivates platelet COX o Platelets cannot synthesise new COX: Takes 4 – 7 days for new platelets to be synthesised following a single dose (300mg) Reduction in production of the platelet aggregating compound thromboxane A2 • Adverse effects: o Bleeding o Bronchospasm o GI irritation / bleeding o Dangerous in overdose • Overdose: o Signs / symptoms: Coma Dehydration Hyperventilation Tinnitus Seizures Sweating Vertigo Vomiting o Investigations: Levels (salicylate and paracetamol, may have taken both): • Levels >700mg/L are potentially fatal ABG, FBC, Glucose, LFTs, INR, U&Es o Treatment: Remove drug: • Gastric lavage if od 500mg/L: • Consider alkalinization of the urine Consider dialysis when: • Levels >700mg/L • Cardiac / renal failure • Seizures • Cautions: o Asthma o Uncontrolled hypertension • Contraindications: o Children 12 months o Coronary artery stents Copyright Dr Garry KJ Pettet 2005 - 2009 62 www.garrypettet.com 66. • Mechanisms of action: o Irreversibly blocks the action of ADP on platelets – leading to a reduction of platelet aggregation • Adverse effects: o Bleeding o Bone marrow

suppression (rare) • Cautions: o First few days following MI / CVA • Interactions: o Warfarin: Increased risk of bleeding Abciximab: • Indications: o Patients awaiting PTCA: Short-term prevention of MI in those with ACS o Patients undergoing PTCA: Adjunct to aspirin and heparin • Mechanism of action: o Monoclonal antibody to GP IIb/IIIa o Inhibit platelet aggregation • Adverse effects: o Bleeding o Thrombocytopenia Warfarin: • Indications: o Prevention / treatment of VTE: DVT PE o Prevention of thromboembolism: AF Prosthetic heart valves • Mechanism of action: o Vitamin K antagonist o Inhibits the vitamin K-dependent synthesis of clotting factors II, VII, IX and X o Also inhibits formation of protein C and S: Has an initial procoagulant effect o Takes at least 2–3 days to work (due to the half-life of pre- existing clotting factors in the circulation) o Prolongs the prothrombin time (PT) • Pharmacokinetics: o Long half-life (40 hours) o Takes ~5 days after stopping treatment for INR to normalise o Highly protein-bound (albumin) • Dosage: o Loading: Warfarin therapy begins with a loading dose, usually: Copyright Dr Garry KJ Pettet 2005 - 2009 63 www.garrypettet.com 67. • Day 1 - 10mg • Day 2 – 10mg measure INR and adjust dose • Day 3 – 5mg (if still not target INR) o Daily dose: Daily maintenance is usually 3-9mg daily (taken at same time each day) • INR (International Normalised Ratio): o Prothrombin results can vary depending on the thromboplastin reagent used o The INR is a conversion unit that takes into account the different sensitivities of thromboplastins o Target INRs: 2 – 2.5: • Prophylaxis of DVT 2.5: • AF • Treatment of DVT / PE • Rheumatic mitral valve disease 3.5: • Recurrent DVT / PE • Mechanical prosthetic heart valves o Monitoring the INR: The INR should be determined daily (or alternate days) in the early days of therapy, then at longer intervals (depending on response) then up to every 12 weeks • Adverse effects: o Bleeding / bruising o Skin necrosis o Alopecia o Liver damage o Pancreatitis • Management of warfarin-induced haemorrhage: o Major bleeding: Stop warfarin Give vitamin K (phytomenadione) by slow IV injection FFP o INR >8 (no bleeding or minor bleeding): Stop warfarin and restart when INR