Aspirin and the Salicylates

K. D. Rainsford, PhD, MRCPath
Senior Research Associate
Department of Pharmacology, University of Cambridge, Cambridge
Honorary Lecturer in Chemical Pathology
King's College Hospital Medical School,
University of London, Denmark Hill, London
Visiting Reader in Pharmacology
Department of Biochemistry, University of Surrey, Guildford
Contents

Abbreviations and Nomenclature ix

1 History and Development of the Salicylates:  1

Early use of salicylate-containing plants  1
  Hippocratic era  1
  Roman and Greek medicine  1
  Asia and America  2
  European Middle Ages  2
  Nineteenth century  3

Chemical developments  3
  Isolation and purification of salicylic acid  3
  Synthesis and commercial development of aspirin (acetylsalicylic acid)  7
  Other salicylates  11

2 Occurrence, Properties and Synthetic Developments of the Salicylates  13

Naturally occurring salicylates  13
Commercial synthesis and properties of the salicylates  15
  Salicylic and acetylsalicylic acids, their salts and esters  15
  Salicylamide  16
  Salicylate derivatives  17
    Diflunisal and flufenisal  18
    Benorylate  19
    Meseclazone  19

Experimental drugs  20
  3-Methylsalicylic acid  20
  Aspirin anhydride  21
  Dihydroxy- and diacetoxybenzoic acids  21
  Salicylazosulphapyridine (sulphasalazine) and 5-aminosalicylic acids  22
3 Absorption, Metabolism and Disposition of the Salicylates

Introduction 32
Absorption, Metabolism and Distribution 32
Aspirin, salicylate and their esters 32
Factors influencing absorption 32
Non-enzymic hydrolysis 34
Aspirin esterases and protein acetylation 36
Hydroxylation and conjugation of salicylates 38
Plasma protein binding 41
Factors influencing drug binding to plasma proteins 42
Binding characteristics 42
Binding sites for salicylate on albumin 44
Protein binding in relation to pharmacokinetics 45

Absorption and elimination kinetics 45
Drug formulations 47
Aspirin–Drug interactions 49

Diflunisal 50
Benorylate 51
Salicylamide 53
Salicylazosulphapyridine (sulphasalazine) 53
Salicylsalicylic acid (diplosal, salysal, salsalate) 55
Percutaneous absorption of salicylate esters and other derivatives 55
Experimental pro-drugs 55

Analytical Methods 56
Colorimetric and spectrophotometric procedures 56
Spectrofluorimetry 57
Thin-layer chromatography 57
Gas–liquid chromatography 57
High pressure (performance) liquid chromatography 58
Determination of glucuronides and sulphate metabolites 58

4 Pharmacological and Biochemical Actions of the Salicylates 67

Introduction 67
Anti-inflammatory effects 69
Studies in animal models 69
Acute inflammatory models 71
Contents xvii

Paw oedema assays 71
Pleurisy, air-bleb and sponge-implantation models 73

Actions of salicylates in acute inflammatory models 73
  Comparative effects of different drugs 73
  Role of mediators of the inflammatory response 75
  Structure–activity relationships 78

Chronic adjuvant polyarthritis (rats) 82
Comparative effects of salicylates and other NSAI drugs in adjuvant arthritis 87
Biochemical and cellular responses of salicylates in adjuvant disease 88
Actions of salicylates in other chronic models of inflammation 90
Biochemical effects of salicylates in relation to their anti-inflammatory actions 91
  Synthesis and metabolism of prostaglandins, thromboxanes and leukotrienes 91
  Effects of salicylates on prostaglandin production 96
  Actions of salicylates on 12-HETE and leukotriene production 99
  Effects of salicylates on free radical production 100

Early-phase amines and kinins 101
  Histamine 102
  Serotonin 102
  Kinins 103
  Lysosomal enzymes 103

Endothelial damage, leucocyte migration and platelet accumulation 106
  Platelet aggregation and thrombus formation 106
  Mechanisms of inhibition of platelet aggregation by salicylates 107
  Comparison of the anti-aggregatory properties of different salicylates: importance of chemical structure 109
  Thrombolytic/fibrinolytic activity 111
  Chemotaxis of polymorphs and monocytes 112

Displacement of albumin-bound peptides and tryptophan 113

Connective tissue metabolism 113
  Metabolism of glucose 115
  Production of ATP 115
  Synthesis of connective tissue proteoglycans and glycoproteins 118
  Anti-proliferative activities 122

Lymphocyte transformation and functions 123

Analgesic activity 123
  Introduction 123
    Mechanisms of pain responses 124
    Comparative effects of salicylates in pain models in animals 124
    Mechanisms of analgesia 126
      Responses in central and peripheral nerves 126
Contents

Prostaglandins 126
Serotonin production in the CNS 127
Actions on nerve membranes and functions 127
Other biochemical changes 129

Anti-pyresis 130

Comparative efficacy of different salicylates 130
Mode of actions of salicylates 130

5 Side-Effects and Toxicology of the Salicylates 148

Introduction 148
Gastrointestinal side-effects 151

Historical 151
Aspirin as a major cause of bleeding and ulceration 152
Gastrointestinal side-effects from salicylates in arthritic patients 154
Assessment of gastrointestinal damage in man 156

Gastroscopy and gastrointestinal blood loss methods 156
Intragastric cell exfoliation 159
Gastrointestinal protein loss 160
Intragastric bleeding 160

Factors affecting gastrointestinal damage 161
Acidity of the gastric contents 161
The presence of food in the stomach 161
Dosage and timing of drug ingestion 161
Oral versus parenteral effects of salicylates 162
Blood group status, race, age and sex 163
Exacerbation by alcohol (ethanol) 163
Vitamin C (ascorbate) deficiency 164

Site and pathology of lesions 164
Studies in laboratory animals 165

Procedures for assessment of gastrointestinal damage 165
Comparison of the gastro-intestinal damage by different salicylates 172

Factors influencing gastric ulcerogenicity 176
Alcohol consumption 176
Disease psychophysiological stress 176
Nutritional status 177
Vitamin C status 179
Dosage, route and timing of drug administration 180
Sex and age 184
Particle size of drug 185
Physicochemical and structural features of salicylates 185

Comparison of some of the factors influencing gastric mucosal damage by aspirin in man with those in laboratory animals 187

Intestinal damage 188
Pathology of salicylate-induced gastrointestinal damage 189
The gastric mucosa 189
The intestinal mucosa 200

Mechanisms of gastric mucosal damage by salicylates 201

**Primary changes** 201
- Effects of the mucosal barrier 201
  - Disruption of mucus and mucosal cells 202
  - Capillary damage 204
- Effects of salicylates on mucosal blood flow, acid secretion and $H^+$ ion back diffusion 206
- Pepsin and lysosomal mucosal autodigestion 213
- Prostaglandin inhibition and mucosal cytoprotection 214

**Secondary changes** 218
- Reduction in mucus 218
- Mucosal detoxification 219
- Cell turnover and mucosal protein and nucleic acid syntheses 220

**Tertiary changes** 221

Summary 221

Nephropathy 221
- Analgesic abuse syndrome 222
- Studies in arthritic patients 225
- Pathology 226
- Biochemical effects of salicylates 229
  - Factors influencing drug distribution and actions 229
  - Prostaglandins, kinins, the renin–angiotensin system and renal functions 231
  - Renal intermediary metabolism and biosynthesis of macromolecules 232

Hepatotoxicity 233
- Clinical evidence 233
- Pathology and biochemical changes 235

Hypersensitivity reactions and asthma 236
- Aspirin-sensitive asthma 237
- Urticaria and angioedema 240

Teratogenesis and pregnancy 241

Miscellaneous side-effects 243

Acute salicylate poisoning 245
- Toxic manifestations 245
  - Central nervous system (CNS) effects 245
  - Gastrointestinal effects 246
  - Metabolic effects and acid–base balance 246
  - Vomiting and electrolyte imbalance 247
  - Pulmonary oedema 247
  - Renal damage 247
6 Therapeutic Uses of the Salicylates 272

Introduction 272
Arthritic conditions 273
Rheumatoid arthritis 273
Aspirin, salicylate and their esters compared with acidic NSA1 drugs 275
Salicylazosulphapyridine (sulphasalazine) 278
Other salicylates 278

Osteoarthritis (osteoarthrosis) 279
Miscellaneous 280
Gout 280
Still's disease (juvenile rheumatoid arthritis) 281
Systematic lupus erythematosus (SLE) 281
Rheumatic fever 281

Drug monitoring 281
Interactions with other anti-inflammatory drugs 282

Analgesia 284
Assessment of pain 284
Migraine and headache 284
Acute surgery 286
Postpartum and episiotomy 287
Dysmenorrhoea 288
Cancer 289

Anti-pyresis 289
Thromboembolic conditions 290

Perturbed metabolic states 293
Diabetes mellitus 294
Thyroiditis and thyrotoxicosis 295
Bartter's syndrome 296
Obesity 296
Cystic fibrosis 297

Other possible uses 297
Dermatological conditions 297
Diarrhoea 298
Ductus arteriosus 298
Sickle-cell anaemia 298
Thrombocytic thrombocytopenic purpura 299
Anti-tumour activity 300
Prevention of allograft rejection 301
Anti-viral and anti-parasitic activities 301
Multiple sclerosis 302
Miscellaneous 302