Part I

Introduction

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Combination therapy of diseases: general concepts

Emma Mason and Philip A. Routledge

Department of Pharmacology, Therapeutics and Toxicology, Wales College of Medicine, Cardiff University, Cardiff, UK

Many drugs are excellent when mingled and many are fatal

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Historical aspects

Combination therapy has been used since therapeutics was first practiced. The physician or *asu* of Mesopotamia in 1700 BC used combinations of several plants, minerals and animal products in concoctions, salves and fomentations (Lyons and Petrucelli, 1987). We know little of the efficacy or toxicity of these combined medications. However, the Babylonian code of Hammurabi states that a doctor who causes the death of a patient or loss of an eye should lose his hands. It would not have been surprising if such stringent punishments encouraged the use of a large number of non-toxic (and possibly non-efficacious) medicines. At least this would have ensured that the physician could continue to be able to mix his own preparations.

Since many early drugs were of plant origin, the use of single herbal preparations containing many potentially active ingredients resulted in combination therapy, albeit often unknowingly. Thus cannabis, advocated by the Red Emperor (Shen Nung) around 2800 BC contains around 30 cannabinoid compounds, and debate still rages today as to whether cannabis has greater therapeutic efficacy than single cannabinoid therapy (e.g. with delta-9 tetrahydrocannabinol) in certain medical conditions. Traditional Chinese medicines continue to be used regularly by up to half the population of China (Encyclopaedia Britannica, 1999), and contain several constituents prescribed in individualized doses in a *bespoke* fashion. The patient takes these ingredients home and boils them in a soup, before consuming the broth.

In 1753, the Scottish physician and sailor, James Lind described one of the first controlled trials of drug therapy in history, which he had performed 6 years earlier. He administered a combination treatment for scurvy containing nutmeg, garlic mustard seed, *rad. raphan*, balsam of Peru and gum myrrh to two sailors for 6 days.

It is not surprising that the sailors who improved most were not these two individuals, but two others given another 'combination therapy' – two oranges and a lemon (Lind, 1753)!

The deliberate combination of medicines continued to be practiced right through into the nineteenth and twentieth centuries, although not embraced by all physicians.

William Withey Gull (1816–1890) particularly condemned prescriptions containing multiple drugs. He was a passionate advocate of the scientific basis of medicine and stated that '*The road to a clinic goes through the pathologic museum and not through the apothecary's shop*'. Drug combinations were often contained in medicines, the contents of which were kept secret from the patient. Dr Pierce's Pleasant Purgative Pills were said to combine the active principles of several unspecified vegetable compounds which 'in some inexplicable manner, gradually changed certain morbid conditions of the system, and established a healthy condition instead' (Pierce, 1891). Dr Pierce did not patent his proprietary medicines as 'cure-alls', but others did patent theirs, since there was little or no government regulation of ingredients or need to verify claims of therapeutic efficacy. It was not until 1938, a year after 105 people died due to an elixir of sulfonamide made up of 70% diethylene glycol that the US government legislation was introduced to ensure labeling of all ingredients and prevention of false claims of efficacy (Routledge, 1998a).

The issue of toxicity of ingredients, which still occurs today (Stephens, 1998) is a reminder that most formulations of medicines contain several ingredients, some of which may rarely cause either dose-related (Type A) or idiosyncratic (Type B) toxicity in certain susceptible individuals. Thus, the active principle may constitute as little as 8% of the weight of a typical tablet, and the remainder may include coating and binding agents, fillers, dyes, preservatives, solubilizing and disintegrating agents (Freestone, 1969). To this extent, combination therapy with several compounds occurs when only one medicine is prescribed, although the other ingredients are inactive in most individuals. However, changes to the formulation may affect bioavailability, and were responsible for an outbreak of phenytoin (diphenylhydantoin) toxicity in Australia when lactose was substituted for calcium sulfate as an excipient (Tyrer *et al.*, 1970).

A scientific basis for the value of combination therapy was established in the 1940s. Waksman had discovered streptomycin as the first compound to be effective in the treatment of tuberculosis (Waksman, 1949). Indeed the efficacy of streptomycin in tuberculosis was the subject of the first published randomized controlled trial in medicine (Medical Research Council (MRC), 1948). It was soon realized that streptomycin monotherapy required the use of large doses, which could cause significant toxicity. The emergence of streptomycin resistance was also soon recognized, and combination therapy was seen to be a possible answer to this serious problem. Thus a trial of para-aminosalicylic acid and streptomycin in pulmonary tuberculosis

Table 1.1 Principles for the development of chemotherapeutic regimens in oncology

1	Each single agent should have activity against the disease
2	The agents should have different mechanisms of action
3	The agents should have non-overlapping toxicity profiles
4	The regimen should combine cell cycle specific and cell cycle non-specific agents

found a reduction in streptomycin resistance from 67% in the streptomycin-only group to 10% in those treated with both agents concomitantly (MRC, 1950).

It soon became clear that similar principles applied to the treatment of malignant cells as to slow-growing pathogenic bacteria such as *Mycobacterium tuberculosis*. This led not only to the use of combination chemotherapy of cancer according to specific principles shown in Table 1.1 (Muggia and Von Hoff, 1997). The first three of these principles are generally applicable to combination therapy in other condition, although some exceptions will be highlighted in this chapter. Before discussing the possible advantages and disadvantages of combination therapy, it is important to define and discuss two terms that have been used in this context, sometimes interchangeably.

Polypharmacy

The term polypharmacy has been in use in medicine for around 40 years. One of the first occasions on which it was used was in the context of multiple drug administration versus hypnosis for surgical patients (Bartlett, 1966). This early paper did not make any suggestion that polypharmacy was a bad practice, but a subsequent review of polypharmacy in America highlighted the potential problems that polypharmacy could produce (Hudson, 1968). Indiscriminate polypharmacy has been identified as a major medical problem in some developing countries and a challenge for the World Health Organisation's action program on essential drugs (Hogerzeil *et al.*, 1993).

The strict definition of the word in *The New Shorter Oxford Dictionary* (1993) is '*the use of several drugs or medicines together in the treatment of disease*'. However this initially rather non-judgemental definition is immediately qualified with the rider '*frequently with the suggestion of indiscriminate, unscientific or excessive prescription*'. Other authors have assumed that the administration of an excessive number of drugs is implicit in the definition (*Online Medical Dictionary*, 1997). This has led to the use of the term rational polypharmacy to distinguish the appropriate use of drug combinations from indiscriminate use of several medicines concurrently (Kalviainen *et al.*, 1993; Reus, 1993; Wolkowitz, 1993). Thus

polypharmacy tends to be a pejorative term for excessive irrational drug use, although the drugs may be being used for a range of medical conditions rather than for a single disease.

Polytherapy

The first record of the use of this term listed on *Medline* was just over 20 years ago (1978) in the context of epilepsy management (Deisenhammer and Sommer, 1978). Since then it has been used predominantly in this therapeutic area, and largely by German, Italian, Spanish and French authors. It has not entered general use in the UK, where combination therapy is generally the preferred term for use of more than one drug for the same condition. The definition in the *Online Medical Dictionary* is '*A therapy that uses more than one drug*'. It thus differs from polypharmacy in that it normally refers to the use of drugs for the same medical condition rather than for a group of existing medical conditions. In the following discussion, we will treat the term polytherapy as synonymous with combination therapy, a term that is more widely accepted across the spectrum of therapeutics and throughout Europe and the USA.

Epidemiology of combination therapy

Although, around 10% of the general population take more than one prescribed medicine, the incidence of combination therapy is even greater in the elderly, in females and in those who have had recent hospital admission (Nobili *et al.*, 1997; Teng Liaw, 1997). Stewart and Cooper reviewed a number of studies and concluded that patients aged over 65 years use on average 2–6 prescribed medications and 1–3.4 non-prescribed medications (Stewart and Cooper, 1994).

The effects of multiple drug administration on the incidence of adverse drug reactions were first studied by May and co-workers in 10 518 patients hospitalized on a general medical service during a 5-year period (May *et al.*, 1977). Their data suggested a disproportionately increased risk of adverse drug reactions for patients, the more drugs they were receiving. A significant proportion of these adverse drug reactions were due to adverse interactions between two or more co-prescribed agents.

In a case-control study by Hamilton and co-workers (who over the 3-year period 1993–1995 studied more than 157 000 patients in the USA) the drug combination most often associated with hospital admission was angiotensin converting enzyme (ACE) inhibitors co-prescribed with potassium replacement therapy. Combinations with inhibitors of drug metabolism (particularly macrolide antibiotics such as erythromycin) formed the next most frequent group of agents associated with increased hospitalization (Hamilton *et al.*, 1998).

Advantages of combination therapy

Efficacy can be enhanced by combination therapy

One of the first indications that the use of more than one agent could be more effective than the use of either agent as monotherapy was in the treatment of severe infections (e.g. bacterial endocarditis) with combinations of penicillin and an aminoglycoside (Wilson *et al.*, 1978). It later became clear that this *synergism* was achieved by a dual action on bacterial growth. Penicillins inhibited cell wall synthesis while the aminoglycoside inhibited protein synthesis. Synergism was also demonstrated between loop diuretics and thiazides, since each acted at a different site on the nephron to reduce sodium and water reabsorption. This combination (e.g. frusemide and metolazone) is still used to produce diuresis in resistant congestive cardiac failure. Thus combination therapy normally involves the use of two or more drugs with different mechanism of action, and therefore normally from different drug classes.

The effects of some drug combinations are merely additive rather than synergistic. Nevertheless, the combination produces more efficacy than the use of each single agent alone and this can be of therapeutic benefit. Patients may now leave hospital after acute myocardial infarction on a beta-blocker, ACE inhibitor, antiplatelet agent (e.g. aspirin) and lipid lowering agent (e.g. statin), all having been shown individually to provide secondary preventive benefit in this situation. In heart failure, ACE inhibitors, beta-blockers and spironolactone have been shown to reduce mortality when added to standard therapy. Ischemic heart disease, heart failure and hypertension are heterogeneous diseases with multiple mechanisms contributing to their pathogenesis. It is therefore not surprising that more than one mechanism of action (and therefore more than one drug) may be needed to treat the underlying problems. In addition, several of these chronic diseases result in multiple end-organ damage and several drugs may be needed to treat the multiple pathologies associated with them.

Monotherapy is effective in only around 50% of hypertensive patients, but efficacy can be increased to around 80% with the judicious use of combination therapy (Mancia *et al.*, 1996). The need for combination therapy is also demonstrated by the hypertension optimal treatment (HOT) study. Depending on the target blood pressure, up to 74% of patients needed more than one drug to achieve the required blood pressure (Hansson *et al.*, 1998; Opie, 1998). It is also interesting to note that in this study, patients randomized to acetylsalicylic acid had significantly reduced rates of major cardiovascular events. Thus combined antihypertensive and antiplatelet therapy is valuable, even though these drugs are producing their beneficial effects in completely different ways.

Anticonvulsant drugs are also thought to have a range of different mechanisms of action, but that the same principles should also apply. Even with carefully instituted

and monitored monotherapy, only 70–80% of patients will achieve satisfactory control of their epilepsy (Jallon, 1997) so that combination therapy may be an option that should be considered.

Combination therapy may help to reduce the incidence and/or severity of adverse drug reactions

Dose-related (Type A) adverse drug reactions are thought to make up around 75% of all adverse drug reactions (Routledge, 1998b). Combinations of medicines with different spectra of adverse drug reactions may therefore allow reduction of dose of each compound to levels that are less likely to produce clinically relevant toxicity. This principle (i.e. that the agents should have non-overlapping toxicity) is one of the underlying reasons for the general use of combination chemotherapy in cancer (Muggia and Von Hoff, 1997). In the case of tuberculosis, the use of triple and quadruple antituberculous chemotherapy has allowed some potentially toxic agents (e.g. ethambutol and pyrazinamide) to be used at lower and therefore safer doses than previously. This approach has also allowed shorter treatment courses, thus reducing duration of exposure to risk of toxicity. In hypertension combinations of low doses of two agents from different classes have been shown to provide additional antihypertensive efficacy, thereby minimizing the likelihood of dose-dependent adverse effects.

Combination therapy can prevent the development of resistance

The experience of treatment of tuberculosis indicated that combination therapy might help to prevent the emergence of resistant bacteria. Chambers and Sande (1996) have elegantly argued that if spontaneous mutation were the major mechanism by which bacteria acquired antibiotic resistance, combination chemotherapy should be effective. They illustrate their argument with the example of a micro-organism that has a frequency of development of resistance to one drug of 10^{-7} and to a second drug of 10^{-6}. In this case, the probability of independent mutation of resistance to both drugs in a single cell would be the product of the two frequencies (i.e. 10^{-13}) making the likelihood of development of resistance extremely small. Such arguments clearly apply to other situations such as oncology where the development of resistance can otherwise limit drug efficacy. They are less relevant to the treatment of other diseases.

Disadvantages of combination therapy

The evidence for the benefits of combined therapy is often poor

At the beginning of the last century, therapeutics was based more on the experience of others, rather than on firm evidence. Thus Wilson was able to state that

although many remedies had been tried and were still in favor for the treatment of epilepsy, the only ones that have any effect are the bromides of potassium, sodium and ammonium. It is interesting to note that 'the best results seem to follow the administration of all three in a combined dose' (Wilson, 1912).

In diabetes, the benefits of combination therapy with a biguanide (e.g. metformin) and sulfonylurea (e.g. glibenclamide), in patients with Type 2 (non-insulin-dependent) diabetes who are inadequately controlled with either agent alone, have been claimed for 40 years. The mechanism of action of these two drug classes is different. Biguanides such as metformin (which first became available in Europe in 1957), work by increasing the action of insulin in peripheral tissues and reducing hepatic glucose output due to inhibition of gluconeogenesis. Sulfonylureas act primarily by potentiating glucose-stimulated insulin release from functioning pancreatic islet beta-cells (O'Meara *et al.*, 1990), although studies of insulin secretion at the same plasma glucose concentrations before and during long-term sulfonylurea therapy have shown increased beta-cell sensitivity to glucose and continuously augmented insulin secretion (Gerich, 1989). However, the evidence for combined therapy sulfonylurea/biguanide was relatively sparse for many years, and rested largely on a single non-randomized observational trial of 108 sulfonylurea failures (Clarke and Duncan, 1965). It was only 30 years later that controlled trials confirmed the benefits of this combination of agents (Hermann *et al.*, 1994; DeFronzo, 1995).

In his article on rational polypharmacy in epilepsy, Richens points out that few randomized placebo-controlled studies have been undertaken to compare the relative merits of monotherapy and combination therapy with respect to seizure control (Richens, 1995). Evidence-based medicine should play an important role in the therapeutics of epilepsy, as it has increasingly done in other areas of disease management.

Toxicity may be greater with combination therapy than monotherapy

One of the principles of combination therapy in cancer is that the agents should have non-overlapping toxicity. Clearly this is not always possible, even in oncology, since many anti-cancer drugs share similar toxicity profiles (e.g. myelotoxicity). It may also be difficult to achieve in other therapeutic areas.

It is possible that combination therapy is a risk factor in the production of sudden unexpected death in epilepsy, although the use of more than one drug may just reflect the severe unstable nature of the epilepsy in such individuals (Nilsson *et al.*, 2001). It is also possible that combination therapy is associated with greater risk of anticonvulsant embryopathy in infants exposed to anticonvulsant drugs in utero, (control frequency 8.5%, monotherapy 20.6%, combination therapy 28.0%) so that the risks from each agent in this situation may be additive (Holmes *et al.*, 2001).

Non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of arthritis can increase the risk of peptic ulcer by around four-fold in patients aged

65 years or older (Griffin *et al.*, 1991). Corticosteroids are also used in some patients with arthritis, particularly rheumatoid arthritis. Piper and colleagues, using the same design and patient database as Griffin, showed that the estimated relative risk for the development of peptic ulcer disease among current users of oral corticosteroids (but not NSAIDs) was 1.1 (i.e. a 10% increase in risk). However, patients concurrently receiving corticosteroids and NSAIDs had a risk for peptic ulcer disease that was 15 times greater than that of non-users of either drug (Piper *et al.*, 1991).

Similarly, compared with non-users of either drug, the relative risk of hemorrhagic peptic ulcer disease among current users of both anticoagulants and NSAIDs was 12.7 (95% confidence interval, 6.3–25.7)(Shorr *et al.*, 1993). However, the prevalence of NSAID use among anticoagulant users was 13.5%, the same as in those who were not using anticoagulants. Thus toxicity of drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone.

Enhanced toxicity of drug combinations may sometimes be due to pharmacokinetic interaction. Herpes Zoster infections are not uncommon in immunocompromised patients, and anti-viral agents may be required. Unfortunately 19 people with cancer and Herpes Zoster died in Japan in 1993 because of fluoro-pyrimidine toxicity, caused by the inhibition of 5-fluorouracil metabolism by the metabolite of a new anti-viral agent, sorivudine. Sixteen of the deaths occurred after the drug had been licensed, illustrating that not all drug interactions may be recognized before marketing and widespread exposure to the offending combination of agents occurs (Watabe, 1996).

In 1997, Mibefradil (Posicor) was marketed in the USA and Europe for the treatment of hypertension and angina as an exciting new molecule that selectively blocked T-calcium channels (Frishman, 1997). It was already known before marketing that mibefradil inhibited the metabolism of three potentially toxic agents, astemizole, cisapride and terfenadine. Soon further clinically significant interactions with cyclosporin and tricyclic antidepressants were being reported. It was known that mibefradil could inhibit the action of cytochrome P450 3A4 and thus reduce the clearance of other drugs that were metabolized by this enzyme. In December 1997, because of seven reports of statin-induced rhabdomyolysis in patients receiving simvastatin and mibefradil, lovastatin and simvastatin were added to the list of those that should never be co-administered with mibefradil. This was of particular importance, since hypertension and hypercholesterolemia are important and often co-existing risk factors for ischemic heart disease.

Finally, as a result of the number of serious interactions, the manufacturers announced the withdrawal of mibefradil from the market in 1998; almost exactly a year after the drug had been given marketing approval (Po and Zhang, 1998). Recently Wandel and co-workers have used a human intestinal cancer-derived cell which expresses P-glycoprotein to show that mibefradil is not only a substrate for

P-glycoprotein, but may well be a potent inhibitor of this efflux pump mechanism (Wandel *et al.*, 2000). Thus its combined effects on CYP3A and P-glycoprotein could explain the magnitude of the effect of its interactions with other drugs. Thus the clinical significance of potential interactions may not be fully realized until after marketing.

Combination therapy may be associated with increased risk of non-compliance (non-concordance)

Compliance with therapy is an essential prerequisite of obtaining the benefits of the drugs. The use of combination therapy means that the patient has to take more tablets, unless the drugs have been formulated in a combined preparation. If two drugs are being used in combination, the dose of each should be adjusted to achieve optimal benefit. Thus, patient compliance is essential, yet more difficult to achieve. If patients perceive that they are being overmedicated, they self-report that their compliance falls (Fincke *et al.*, 1998). Polypharmacy may thus result in poor compliance, which may itself result in failure of therapy. This mechanism has been reported to be a problem in individuals with epilepsy (Lambie *et al.,* 1981), and an important factor precipitating admission to hospital for seizure (Lambie *et al.*, 1986).

To obviate the problem of multiple medication use, many fixed-dose drug combinations are marketed. The use of such combinations is advantageous only if the ratio of the fixed doses corresponds to the needs of the individual patient. In the USA, a fixed-dose combination of drugs is considered a 'new drug' and as such must be approved by the Food and Drug Administration (FDA) before it can be marketed, even though the individual drugs are available for concurrent use. To be approved, certain conditions must be met. Either the two drugs must act to achieve a better therapeutic response than either drug alone (e.g. many antihypertensive drug combinations); or one drug must act to reduce the incidence of adverse effects caused by the other (e.g. a diuretic that promotes the urinary excretion of K^+ combined with a K^+-sparing diuretic) (Nies and Spielberg, 1996).

Combination therapy may be associated with an increased risk of medication error

Misuse of medications is a major cause of morbidity and mortality. Patients' medication bottles and their reported use of medications were compared with physicians' records of outpatients in Boston, Massachusetts. Discrepancies were present in 239 patients (76%). The 545 discrepancies in these patients were the result of patients taking medications that were not recorded ($n = 278$ [51%]); patients not taking a recorded medication ($n = 158$ [29%]) and differences in dosage ($n = 109$ [20%]). Older age and polypharmacy were the most significant correlates of discrepancy (Bedell *et al.*, 2000).