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Fixed-dose single tablet antidiabetic combinations

C. J. Bailey and C. Day

School of Life and Health Sciences, Aston University, Birmingham, UK

Combinations of two or more oral agents with different mechanisms of action are often used for the management of hyperglycaemia in type 2 diabetes. While these combinations have customarily been taken as separate tablets, several fixed-dose single tablet combinations are now available. These are based on bioequivalence with the separate tablets, giving similar efficacy to the separate tablets and necessitating the same cautions and contraindications that apply to each active component. Fixed-dose combinations can offer convenience, reduce the pill burden and simplify administration regimens for the patient. They increase patient adherence compared with equivalent combinations of separate tablets, and this is associated with some improvements in glycaemic control. Presently available antidiabetic fixed-dose combinations include metformin combined with a sulphonylurea, thiazolidinedione, dipeptidylpeptidase-4 inhibitor or meglitinide as well as thiazolidinedione–sulphonylurea combinations, each at a range of dosage strengths to facilitate titration. Anticipated future expansion of multiple drug regimens for diabetes management is likely to increase the use of fixed-dose single tablet combinations.

Keywords: antidiabetic agents, bioequivalence, compliance, fixed-dose combinations, hypoglycaemic agents
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Introduction

The management of hyperglycaemia in type 2 diabetes often requires a combination of two or more glucose-lowering therapies [1,2]. These can be used to improve glycaemic control by addressing different pathophysiological aspects of the disease, such as insulin resistance, β-cell dysfunction, α-cell dysfunction and defects of nutrient metabolism affecting liver, muscle and adipose tissue [3,4]. With increased attention focussed towards glycaemic targets and the prevention of complications [2,5–7], there has been heightened interest in combination therapy, particularly 'fixed-dose' single tablet combinations of antidiabetic agents. This review takes stock of the current use and future opportunities for antidiabetic single tablet combinations.

Use of Antidiabetic Combinations

Although the most desirable target for good glycaemic control remains in contention, there is much evidence to demonstrate that better glycaemic control, especially during early stages of the disease process, helps to reduce long-term morbidity and mortality [8–10]. Most treatment algorithms for type 2 diabetes acknowledge this as a basis for their choice of target [2,5–7]. They also emphasize lifestyle (diet and exercise) advice as initial and ongoing therapy and generally suggest metformin as a first-line pharmacological agent, provided there are no contraindications or tolerability issues [2,5–7]. If appropriate, another type of antidiabetic agent such as an insulin secretagogue, thiazolidinedione or an α-glucosidase inhibitor could be used. However, one antidiabetic agent alone is rarely sufficient to maintain acceptable glycaemic control. For example, in the United Kingdom Prospective Diabetes Study, less than one-quarter of patients treated with a single oral antidiabetic agent maintained a glycosylated haemoglobin A1c (HbA1c) level below 7% after 9 years [1]. When one agent does not achieve or sustain the desired glycaemic target, it is customary to add a second agent. If patients exhibit severe hyperglycaemia, this usually indicates the need for

Correspondence:
Prof. Clifford J. Bailey, School of Life and Health Sciences, Aston University, Birmingham B4 7ET, UK.
E-mail:
c.j.bailey@aston.ac.uk

insulin therapy which can be introduced while continuing one or more oral agents (figure 1).

Prescription databases in the UK such as DINLink and MAT indicate that in 2007 about one-third of all patients with diagnosed type 2 diabetes are treated with two or more oral antidiabetic agents. A recent survey of 154 general practices in the UK (covering 1.2 million people, 3.1% diagnosed type 2 diabetes) noted that 36.8% of type 2 patients were being treated with two or more oral antidiabetic agents [11]. The oral combination therapy 'bought' a median 7.7 years of time after monotherapy until initiation of insulin therapy. Prescription databases for the UK in 2007 indicate that among type 2 diabetes patients who are receiving oral antidiabetic drugs, just over 50% are treated with monotherapy, just over 40% are treated with a combination of two oral agents and about 4–5% are prescribed three types of agents.

Combinations of Antidiabetic Agents

The potential benefits and extra cautions associated with a combination of two or three antidiabetic agents have been rehearsed in detail previously [12,13]. As a rule of thumb antidiabetic agents with *different* modes of action can be used in combination to achieve additive or possibly synergistic glucose-lowering effects. In principle, these differently acting agents should address different pathological factors, thereby increasing therapeutic breadth to combat the progressive nature of type 2 diabetes. Where lower doses of two agents can be used instead of a high dose of one agent, this can reduce the side effects that often occur with a high dose of the one agent [12,13]. However, combination therapy requires that the contraindications, precautions and monitoring associated with each agent must be respected. Risk of hypoglycaemia, possible drug interactions and special care during dose titration must also be appreciated.

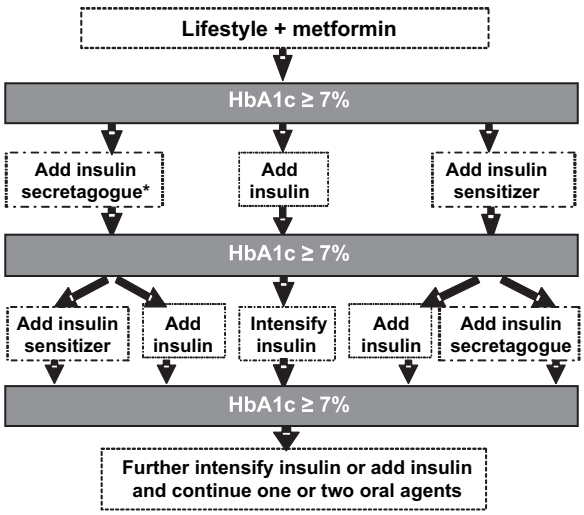

Fig. 1 Simplified algorithm for the treatment of hyperglycaemia in type 2 diabetes. Modified from the American Diabetes Association - European Association for the Study of Diabetes (ADA-EASD) consensus statement [2].
*Insulin sectetagogue could be a sulphonylurea, meglitinide, DPP-4 inhibitor or GLP-1 agonist. An α-glucosidase inhibitor can be added with any of the other antidiabetic therapies

In practice, metformin can be combined with any other therapy (unless contraindications exist). Commonly, an agent that reduces insulin resistance (e.g. metformin or a thiazolidinedione) is combined with an oral insulin secretagogue, such as a sulphonylurea or meglitinide [2,5]. Combination with one of the newly available secretagogues, namely a dipeptidylpeptidase-4 (DPP-4) inhibitor or an injectable glucagon-like peptide-1 (GLP-1) agonist, is also a viable option [14]. Additionally, because metformin and thiazolidinediones counter insulin resistance by different cellular mechanisms, these agents can be combined with additive antihyperglycaemic efficacy [15]. Where extra postprandial control is required, or interprandial glycaemic troughs are too low, an α-glucosidase inhibitor can be combined with any other antidiabetic therapy [12]. Because sulphonylureas act on the beta-cell by a different cellular mechanism to GLP-1, sulphonylureas have also been combined with a GLP-1 agonist or DPP-4 inhibitor [14].

The effect of adding a second antidiabetic agent has been assessed in many prospective randomized double-blinded placebo-controlled or parallel group comparator studies: these are summarized and reviewed elsewhere [12–16]. When interpreting these studies, it is pertinent to bear in mind the variability of individual responses and disease status. Thus, the falls in HbA1c vary with recruited population, baseline HbA1c, obesity, drug doses and treatment duration as well as the actual agents involved, making it difficult to compare add-on efficacy between studies [12,13,16]. Oral combinations are sometimes continued with the introduction of insulin in type 2 diabetes [17]. These usually include an agent to reduce insulin resistance, but an insulin secretagogue can increase endogenous insulin delivery into the portal vein to target the liver. This complements the higher peripheral insulin levels achieved with subcutaneous injections.

Reassuringly, most treatment guidelines offer some practical advice about individualizing combination therapy, heeding exclusion criteria and minimizing risk of hypoglycaemia if close to a low glycaemic target. Other prominent considerations include weight gain, co-existing morbidity, vascular risk, patient lifestyle and potential interactions with other medications [2,5–7].

Compliance Problems

Although oral combination therapy has mostly been undertaken with separate tablets for each agent, this increases the pill burden for a group of patients who are already likely to be treated with several other medications [18]. Many type 2 patients take more than 10 medications daily and some take in excess of 20 [18–20]. Several studies involving agents to treat hypertension and dyslipidaemia have noted that patient adherence declines as the number of prescribed medications increases [21,22]. Careful tracking of antihypertensive therapy using containers with electronic date–time recorded dispensing noted that compliance (percentage of days on which the prescribed numbers of doses were removed) decreased from 83 to 57% when comparing once-daily vs. thrice-daily therapy [23].

Adherence to oral antidiabetic therapies is similarly prone to decline with increases in dosage frequency and number of daily medications [24–26]. For example, in 91 type 2 patients, compliance (defined as percentage of prescribed doses reportedly taken by patients) with oral antidiabetic therapy fell from 79% for a once-daily dose to 38% for three times daily [27]. In the Diabetes Audit Research in Tayside (DARTS, Scotland) study of 2849 type 2 diabetic patients, adherence (measured as refilling $\geq$90% of prescribed medication for >1 year) to sulphonylurea or metformin as monotherapy was 31 and 34%, respectively, corresponding to about 300 days of treatment per year. When a combination of these two drugs was prescribed, adherence was reduced to 13%, corresponding to 266 days of treatment per year [28]. A similar study in the USA tracked 6995 type 2 patients for 2 years and noted that compliance (defined as the number of days for which tablets were collected) for sulphonylurea or metformin as monotherapy was 60.5 and 63%, respectively, corresponding to 435 and 454 days of treatment over 720 days. However, compliance was only 35.7% (corresponding to 257 days of treatment over 720 days) when the drugs were prescribed as a combination [29]. One might anticipate therefore that improvements in glycaemic control expected by treatment intensification could be at least partially offset by reduced adherence.

Fixed-dose Combinations of Antidiabetic Tablets

Fixed-dose single tablet combinations of antidiabetic agents offer several potential advantages over separate tablets, particularly associated with compliance. They also impose the same cautions associated with separate tablet combinations.

Advantages

Single tablet combinations of antidiabetic agents can increase adherence compared with separate tablets. For example, a US prescription database was used to assess adherence (proportion of days for which tablets were collected) during 1 year by 1618 diabetic patients switched from monotherapy with metformin or rosiglitazone to a combination of these agents. Patients receiving a fixed-dose combination (Avandamet) showed greater adherence (86%) than those receiving a combination of separate tablets (61%) [30]. In a study of 6525 newly diagnosed patients treated with either glibenclamide (glyburide) or metformin monotherapy, adherence (proportion of days for which tablets were collected) over 6 months was similar for the two agents at 71% [31]. However, when patients required combination therapy, those given separate tablets showed only 54% adherence, whereas adherence was maintained (77%) among those given a fixed-dose combination. Moreover, improved adherence translates into improved glycaemic control: thus, when 72 patients receiving metformin and glyburide as separate tablets were switched to a fixed-dose single tablet regimen, HbA1c was reduced by 0.6% [32].

Improved adherence implies less drug wastage and greater opportunity for added agents to achieve their therapeutic potential. Indeed, increased adherence to antidiabetic medication correlated with fewer hospital admissions and reduced overall healthcare costs among type 2 patients [33]. Also, a recent retrospective study of adherence (proportion of days for which tablets were collected) to all therapies in 11 532 diabetic patients noted higher HbA1c, higher blood pressure and higher LDL cholesterol levels in non-adherent patients (<80% of tablets collected), and this coincided with increased risk of hospitalization and increased mortality [34].

Because many individual antidiabetic drug therapies are administered with the same dosing schedules, there is a pharmacokinetic rationale for their combination within single tablets. It is sometimes argued that fixed-dose combinations reduce prescriber flexibility and constrain the titration process, but there are several different dosage strengths of most fixed-dose combinations (table 1), which facilitate and simplify dose titration. Also, as with combinations of separate tablets, fixed-dose combinations can facilitate similar or greater glycaemic control with lower doses of two agents than with a large dose of one agent. For example, a fixed-dose metformin–glipizide combination (Metaglip) produced

Table 1 Fixed-dose single tablet antidiabetic combinations*†

Tablet®	Components	Strengths (mg)
Glucovance	Metformin + glibenclamide‡	250:1.25; 500:2.5; 500:5.
Metaglip	Metformin + glipizide	250:2.5; 500:2.5; 500:5.
Avandamet	Metformin + rosiglitazone	500:1; 500:4; 500:2; 1000:2; 1000:4
Competact** Actoplusmet	Metformin + pioglitazone	500:15; 850:15
Eucreas	Metformin + vildagliptin	850:50; 1000:50
Janumet	Metformin + sitagliptin	500:50; 1000:50
Prandimet††	Metformin + repaglinide	500:1; 500:2
Avaglim** Avandaryl	Rosiglitazone + glimepiride	4:1; 4:2; 4:4; 8:2; 8:4
Tandemact** Duetact	Pioglitazone + glimepiride	30:4; 45:4

*Based on Bailey [56].
†Availability of tablets and component strengths differ between countries.
‡Glibenclamide = glyburide.
**Names vary between Europe and USA.
††Food and Drug Administration (FDA) approval June 2008.

more than twice the reduction of HbA1c compared with similar or greater dosages of metformin or glipizide as monotherapy [35]. Similarly, a fixed-dose combination of metformin–glibenclamide (Glucovance) achieved a greater reduction in HbA1c with half or less than half of the amounts of metformin or glibenclamide as monotherapy [36]. The extra glucose-lowering effect seen with the Glucovance fixed-dose combination may have been achieved in part through a small adjustment in the formulation (discussed below), indicating a further opportunity to increase the efficacy gain from fixed-dose combinations.

As reported with combinations of separate tablets, lower doses of two agents in a fixed-dose combination can reduce the side effects associated with a high dose of one agent. Thus, uptitrating metformin to improve glycaemic control may be limited by onset of diarrhoea, but this was avoided while achieving a similar improvement in glycaemic control by addition of rosiglitazone in a fixed-dose combination [37].

From a pharmacoeconomic perspective [38], some drug cost reimbursement procedures may enable patients and/or their healthcare providers to use fixed-dose combinations to receive two drugs for approximately the price of one. Many fixed-dose combinations are priced little higher than the more expensive component of the combination: the cheaper component is usually generic and available as a separate tablet at much lower cost. Thus, fixed-dose combinations are generally competitively priced compared with the same combinations as separate tablets.

Disadvantages

All forms of combination therapy require special vigilance to comply with the contraindications, precautions and monitoring that apply to both agents. Interactions between the different classes of antidiabetic agents are rare [16], but a potentially heightened risk of hypoglycaemia must be appreciated, especially when aiming for near-normal levels of glycaemia. Appropriate selection of the combination and the starting dose should take this into account, noting that agents that do not usually precipitate hypoglycaemia as monotherapy may nevertheless act together to lower glycaemia into the subnormal range. Subtle adjustments to the dose or timing of administration of one of the agents to avoid such events cannot be made with fixed-dose combinations.

Marketing approval of fixed-dose antidiabetic combinations has been based on pharmacokinetic and pharmacodynamic equivalence to the two active components as separate tablets. Although bioavailabilities of the active components may have been adjusted slightly to facilitate administration within the same tablet, the range of dosage strengths available has ensured that concerns about a lack of flexibility for dose titration are seldom a practical limitation. Thus, the dosage increments are generally the same for a fixed-dose combination as separate tablet combinations. The titration steps are dictated by the component that exerts the faster blood glucose-lowering effect, noting that the slowly generated antihyperglycaemic action of thiazolidinediones warrants some extended titration checks.

Certain intercurrent illnesses or investigations may require temporary withholding of one component of a fixed-dose combination, or the emergence of a contraindication may necessitate permanent cessation of one component. In each case, stopping the fixed-dose tablet inconveniently stops both components, but the continuing component can still be given as a single tablet at the same dosage or where appropriate, an alternative combination can be substituted at a comparable strength.

Examples of Fixed-dose Antidiabetic Combinations

The main fixed-dose single tablet combinations of antidiabetic drugs are listed in table 1. Not all combinations or dosage strengths are available in all countries, and there

are some variations in the names and approved indications.

Combination therapy with a biguanide and a sulphonylurea as separate tablets has been used in Europe for over 40 years, and some early fixed-dose combinations involving phenformin or metformin together with a sulphonylurea receive minority use in some countries. However, these combinations were mostly designed around the sulphonylurea component, whereas the introduction of Glucovance (metformin–glibenclamide) as a fixed-dose combination in the USA in 2000 provided a more equitable balance of dosages [36,39]. Glucovance generated a new interest in antidiabetic fixed-dose combinations and accounted for about 6% of oral antidiabetic prescriptions in the USA for 2006, with much higher usage in some countries of central and South America (http://www.come2merck.com/servlet/PB/show/1649970/Merck_GB_06_en_13_b_Ethicals.pdf). Following in the wake of Glucovance, a metformin–glipizide combination (Metaglip, 2002) received much less use [35,39].

Fixed-dose combinations of metformin with the thiazolidinedione rosiglitazone (Avandamet, 2002) or pioglitazone (Competact/Actoplusmet, 2005) have received considerable use in North America. The single tablet combinations show bioequivalence to the two drugs given as separate tablets, affording similar levels of glycaemic control and fewer tolerability issues when used instead of a high dose of one [40,41]. Fixed-dose combinations of a thiazolidinedione with a sulphonylurea have recently been produced, again showing similar properties to the separate tablet combinations (Avaglim/Avandaryl and Tandemact/Duetact) [42,43].

The DPP-4 inhibitors sitagliptin and vildagliptin increase glucose-stimulated insulin secretion, reduce glucagon secretion and improve glycaemic control without weight gain [44]. Fixed-dose combinations of sitagliptin–metformin (Janumet) and vildagliptin–metformin (Eucreas) have been developed [45,46]. Janumet is available in the USA (2007) and due for launch soon in Europe, while Eucreas is available in parts of Europe (2008) but not in the USA. Recently (2008), Food and Drug Administration (FDA) approved a fixed-dose combination of metformin with repaglinide (Prandimet) [47].

Formulation

In some trials, the glucose-lowering effect of Glucovance (noted above) appeared to be slightly more than additive (sometimes described as synergistic) compared with metformin and glibenclamide as separate tablets [36]. However, to provide bioequivalence with the separate tablets, the formulation of Glucovance contains sufficient very small particles of glibenclamide that there is rapid absorption of a small proportion of the glibenclamide. When the combination tablet is taken with or immediately before a main meal, this increases the prandial insulin response, adding particularly to the reduction in postprandial hyperglycaemia [36,48]. Thus, minor adaptations in the formulation of fixed-dose combinations can provide efficacy gains.

Formulation adjustments can also be used to assist tolerability: for example, use of a slow release fixed-dose formulation that combines metformin–pioglitazone can delay absorption of the metformin component and reduce gastrointestinal side effects [49].

Other Fixed-dose Combinations

With regard to the treatment of diabetes and related cardiometabolic disorders, the UK and other European countries have embraced the concept of fixed-dose combinations with less enthusiasm than the USA. Nevertheless, fixed-dose combinations of antihypertensive drugs have been reported to improve compliance and increase efficacy with fewer side effects [50–52]. Multiple therapies are often required to treat dyslipidaemia [53], and several fixed-dose combinations of lipid-lowering agents are approved in various countries, for example Vytorin (ezetimibe–simvastatin), Advicor (lovastatin–niaspan), Simcor (simvastatin–niaspan) and Tredaptive (nicotinic acid plus laropiprant – to reduce the nicotinic acid flush). In recent years, the prospect has emerged that fixed-dose combinations could be used to treat across different indications. For example, Caduet (atorvastatin–amplodipine) provides a single tablet to address lipid-lowering and antihypertensive therapy.

Future Combinations

Development of fixed-dose combinations containing an antidiabetic agent plus a statin has been investigated, and there is ongoing research into combinations of anti-obesity agents. It is generally appreciated that the treatment of type 2 diabetes requires attention to myriad cardiovascular risk factors, and several long-term trials have demonstrated the benefits of adopting this approach [54]. This has fostered the concept of a multiple combination pill (so-called polypill) for diabetes that might be anticipated to include a statin, an antihypertensive, possibly an anticoagulant and one or more antidiabetic

agents in a single tablet. Other ingredients have also been considered in a similar manner to a multivitamin and mineral supplement, but the concept remains futuristic [55]. Since some potential components such as metformin give rise to bulky tablets, possible alternatives include flavoured chewable tablets, sachets of dissolvable agents or liquid formulations.

Conclusions

Fixed-dose combinations of oral antidiabetic agents are slowly becoming established as convenient options in the treatment of type 2 diabetes [56]. They can simplify administration and improve compliance, especially for patients taking many different therapies. Fixed-dose combinations provide an expedience for extra medication without extra tablets.

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