Oral hypoglycaemics

When not to use what

BACKGROUND In the 1940s and '50s the first oral hypoglycaemic agents (the sulphonylureas and metformin) became available. These remained the only agents for the next 50 years. Over the last five years three new classes have been released. General practitioners now have a wider range of effective hypoglycaemic agents from which to choose.

OBJECTIVES This article focuses on those patients where particular agents should not be used: ie. 'when not to use what'.

DISCUSSION In general however, it must be remembered that problems with oral hypoglycaemics are rare. The great majority of patients have no problems with their prescribed hypoglycaemic medication.

Pat Phillips, *MBBS, MA(Oxon), FRACP, MRACMA, is Senior Director, Endocrinology, The Queen Elizabeth Hospital, South Australia.* **Jody Braddon,** *BPharm, is a clinical pharmacist at the Drug And Therapeutics Information Service (DATIS), Repatriation General Hospital, South Australia.*

In type 2 diabetes insulin resistance and insulin deficiency contribute to the metabolic disturbance. Fasting hyperglycaemia results from increased liver glucose production. Preprandial hyperglycaemia results from decreased muscle glucose use. Postprandial hyperglycaemia results from inadequate clearance of mealtime glucose input. The five classes of oral hypoglycaemic agents affect different organs *(Figure 1):*

- acarbose slows carbohydrate digestion reducing postprandial glycaemia
- metformin decreases insulin resistance in the liver (by decreasing hepatic glucose output) and, to a lesser degree in muscle, reducing fasting and daytime glycaemia
- sulphonylureas and the glitinides (repaglinide) increase insulin secretion reducing glycaemia through the day and postprandially, with repaglinide having a larger postprandial effect
- the glitazones reduce insulin resistance in fat, muscle and, to a lesser degree in the liver, reducing preprandial and fasting glycaemia.

In Australia metformin is the most commonly used oral hypoglycaemic agent; sulphonylureas closely follow and the newer agents are not yet widely used *(Figure 2).*

All five classes reduce overall glycaemia (HbA_{1C} by 0.5–2% and average blood glucose by 1.5–3 mmol/L). The classes work independently of each other and have additive effects in combination.

Unfortunately all can have significant and potentially dangerous adverse effects and it is important to choose a medication that has minimal risk as well as being effective. The following case studies illustrate 'when not to use what'.

Case 1 — Ruth

Ruth is a regular visitor and is familiar to all five members of your practice. Her major problem is her chronic obstructive airways disease which is aggravated by her continuing to smoke despite all contrary advice 'because it is the only pleasure I have left'. Her medications include regular aerosol glucocorticoids and salmeterol and she requires salbutamol most days.

She also has type 2 diabetes which is reasonably controlled on glipizide 10 mg twice daily and metformin 850 mg three times daily. She has had laser therapy for maculopathy, has microalbuminuria (first voided albumin creatinine ratio 5.4 mg/mmol) but her plasma creatinine is in the normal range at 0.12 mmol/L (range 0.05–0.12). She takes good care of her feet and hasn't had any foot problems.

She is now 70, is not overweight (weight 50 kg, height 1.49 m)* and reasonably active. Her other medications include celecoxib 100 mg twice daily and perindopril 2 mg/day.

You are administering her regular influenza vaccination and you add a pneumococcal vaccine since you note that she has not been given this.

The next day she rings the surgery complaining of pain in the arm where she got her 'pneumonia shot' and later rings again and speaks to you. It is now clear that her pain is more likely to be from myocardial ischaemia (radiating from her

* BMI = $50 \div 1.49^2 = 22.5 kg/m^2$

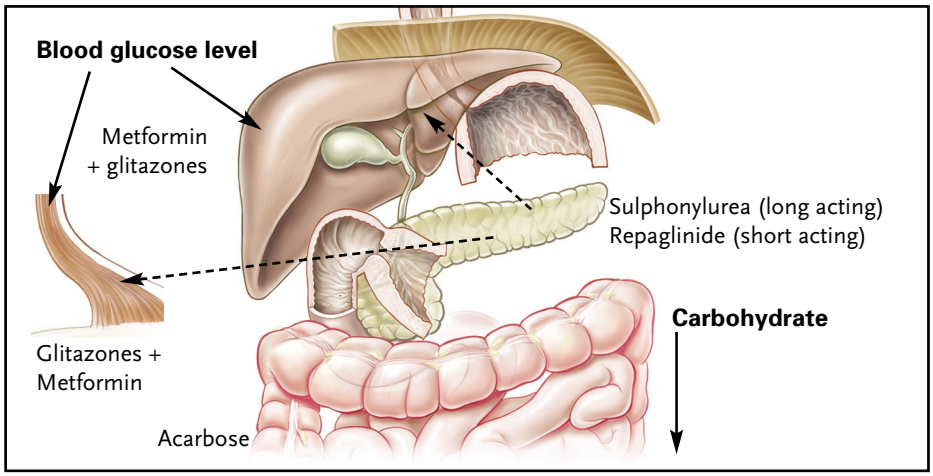

Figure 1. Mechanism of action of oral hypoglycaemic agents.

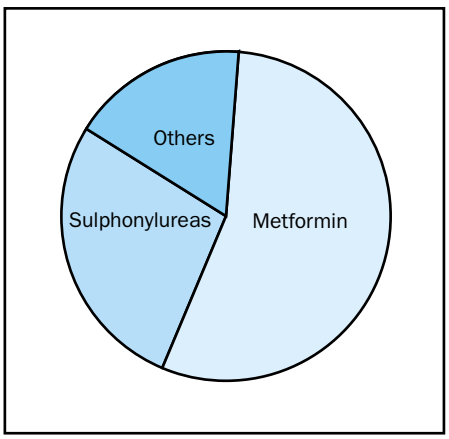

Figure 2. Approximate use of oral hypoglycaemic agents in Australia in 2002.

Table 1. Important contra-indications to metformin therapy

- Renal impairment (see *Table 2* for guidelines)
- Severe hepatic disease[5,20]
- Conditions associated with tissue hypoxia (eg. acute congestive heart failure, recent MI, respiratory insufficiency, septicaemia)[2,5,21,22]
- Others:
  - severe dehydration[2,4,20]
  - acute or chronic alcoholism[20]
  - history of lactic acidosis[5,16]

chest down her arm and into her neck) and you ring an ambulance.

Later that week, at the practice meeting, the senior member mentions that Ruth had indeed had an anterior myocardial infarction but had developed lactic acidosis four hours after admission and had died in intensive care shortly after. Ruth should not have been taking her high doses of metformin because of her renal impairment *(Figure 3)*. Moreover the ACE inhibitor and nonsteroidal are two of the 'triple whammies' which could abruptly worsen her renal function and reduce metformin clearance (the third 'whammy' member class is diuretics).

Metformin

Metformin is now generally considered the drug of first choice in overweight patients with type 2 diabetes who are unresponsive to lifestyle modification alone. The United Kingdom Prospective Diabetes Study (UKPDS) found that intensive treatment of overweight patients with metformin was able to reduce the risk of diabetes related morbidity and mortality.[1] In addition, metformin has favourable effects on body weight and lipid profile, and minimal risk of hypoglycaemia.

However, in some patients and some clinical situations, metformin needs to be avoided due to its association with lactic acidosis.*

Most reported cases of lactic acidosis have occurred in patients who should not have been prescribed this drug *(Table 1)*.[5,9–12] The most commonly overlooked contraindication has been renal insufficiency.[5,10] In addition, a number of cases of metformin induced lactic acidosis occurred when metformin was initiated in a patient with normal renal function, but was not discontinued when renal impairment developed.[13,14]

Before prescribing metformin check the patient's renal function and consider whether there are other problems which might make metformin dangerous to use *(Table 1)*. In elderly patients estimate glomerular filtration rate rather than just considering plasma creatinine measurements *(Figure 3)* because renal function can be abnormal even with a 'normal' plasma creatinine *(Figure 4)*.

There are varying opinions and guidelines with regard to the degree of renal impairment at which metformin should no longer by used.[2,8,9,15,16] Metformin is predominantly renally cleared (by active tubular secretion) and therefore dose adjustment is needed if metformin is going to be considered for patients with some degree of renal impairment.[17,18] Based on the pharmacokinetics of metformin and the current literature we propose the guidelines outlined in *Table 2*.

Renal function should be reassessed every 4–6 months in patients maintained on metformin or more frequently in the presence of other factors that may impair renal function (eg. during the initiation of ACE inhibitors or angiotensin II receptor antagonists, or if NSAIDs or COX-2 inhibitors are coprescribed). Consideration should be given to temporarily withholding metformin in situations in which an acute decline in renal function might occur (eg. when receiving radiographic iodinated contrast media, or in the presence of conditions associated with severe dehydration).[19]

* Lactic acidosis is a rare adverse effect of metformin (incidence 0.03 cases per 1000 patient years)[2,3] but it is fatal in about 50% of cases when it does occur.[2,4] This is a similar fatality rate to sulphonylurea induced hypoglycaemia.[5–7]

When lactic acidosis does occur in people taking metformin, it is often difficult to discern whether it is due to the severe underlying medical disorder or to metformin therapy.[3,18]

Another important consideration when prescribing metformin is that gastrointestinal adverse effects (including diarrhoea, nausea, abdominal pain, anorexia and metallic taste) are common, occurring in up to 30% of patients.[4,9] In most patients these effects are dose related and transient, and can be minimised by administration with meals and gradual dose escalation (eg. start with 250–500 mg once daily and slowly increase it to most effective dose according to tolerance).*

Case 2 — Peter

You have been called to see Peter by his wife Susan because she couldn't wake him. Peter has had type 2 diabetes for many years and has always kept his diabetes under tight control. You suspect hypoglycaemia, his capillary blood glucose is 'LO' (ie. below the meter's measuring range) and he responds to intramuscular glucagon within a few minutes.

There doesn't seem to be any specific cause (in terms of unexpected extra activity or decreased carbohydrate intake). In fact you would have expected his blood glucose to be high rather than low because he has a urinary tract infection. You advise him not to take his hypoglycaemic medication that day and not to undertake any vigorous activity.

Later in the day Susan and her son bring Peter to the surgery because he's acting strangely and seems confused. His blood glucose is again low (2.1 mmol/L) and he responds to a sweet drink and some biscuits. You can't understand what is happening until you check his medication list: glibenclamide 10 mg twice daily,

* From clinical experience, one author (PP) has found that in patients who tolerated metformin but later developed diarrhoea, stopping the metformin may reduce the diarrhoea. The metformin can be reintroduced later.

ESTIMATING RENAL FUNCTION

$$\text{GFR}^* = \frac{(140 - \text{age (years)}) \times \text{lean body weight (kg)}}{1000 \times \text{plasma creatinine (mmol/L)}} \quad (\times 1.22 \text{ for males})$$

For example: For Ruth

$$\text{GFR} = \frac{(140 - 70) \times 50}{120} = 29 \text{ ml/min}$$

* GFR = calculated glomerular filtration rate (mL/min)

Figure 3. Estimating renal function.

Table 2. Guidelines for use of metformin in patients with renal impairment

Degree of renal impairment	Recommendation
Mild renal impairment (GFR 60–90 mL/min)	Use smallest dose of metformin which is effective. Do not exceed a maximum of 2 g per day*
Moderate renal impairment (GFR 30–60 mL/min)	Use metformin with extreme care. The dose of metformin needs to be reduced. In general, a dose of 1 g metformin per day should not be exceeded*
Severe renal impairment (GFR < 30 mL/min)	Avoid metformin

*Consider not using metformin if the patient has any other risk factor for lactic acidosis *(Table 1)*

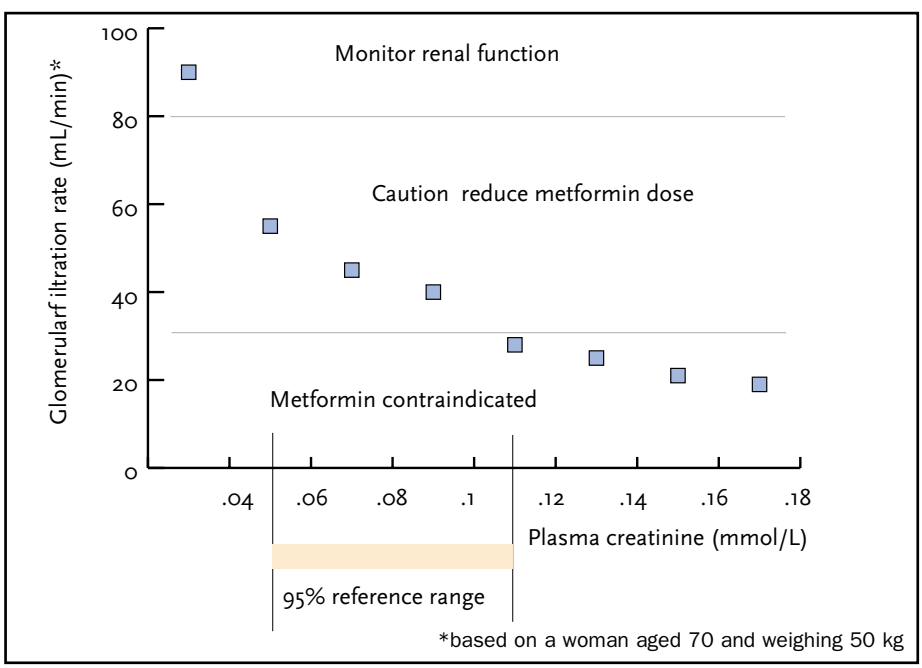

Figure 4. Renal function and plasma creatinine in older people.

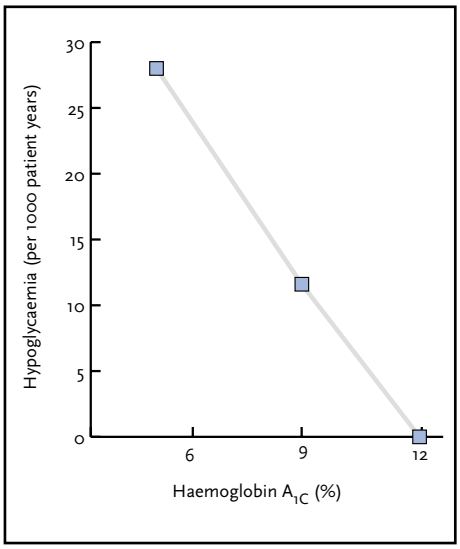

Figure 5. Hypoglycaemia and glycaemic control.

Table 3. Important contra-indications to sulphonylureas

- Severe hepatic impairment[20,34]
- Hypersensitivity to sulphonylureas*[20,34]
- Severe renal impairment[20,34]

* Although theoretically sensitivity to sulphonylureas might be expected in patients sensitive to sulphonamides, this is rarely a clinical problem.[35]

Table 4. Selected drugs that may increase the risk of hypoglycaemia in patients taking insulin secretagogues*

Drugs which lower blood glucose (sulphonylureas or repaglinide)

- Other oral hypoglycaemic agents†
- ACE inhibitors
- Alcohol
- Anabolic steroids
- Perhexilene

Drugs which may increase the plasma levels of insulin secretagogues resulting in an increased risk of hypoglycaemia.

Sulphonylureas:
- Cimetidine
- Fluconazole, ketoconazole, miconazole
- Fluoxetine, fluvoxamine
- NSAIDs

Repaglinide:
- Ketoconazole, fluconazole, itraconazole
- Erythromycin, clarithromycin
- Diltiazem
- Nefazodone, fluoxetine, fluvoxamine

- Sulphonamide antibiotics¥
- Salicylates (high dose only)†† ¥

* This is not intended to be an exhaustive list of all drugs which could potentially interact with sulphonylureas or repaglinide. Note that some of the signs of hypoglycaemia may be masked by beta blockers and clonidine.

† These do not cause hypoglycaemia when used as monotherapy.

†† An interaction is not expected between sulphonylureas and low dose aspirin (ie. antiplatelet doses).

¥ These drugs may interact either pharmacokinetically and/or pharmacodynamically with sulphonylureas.

metformin 500 mg three times daily, perindopril 4 mg/day and the sulfamethoxazole/trimethoprim started for his urinary tract infection.

You suspect an interaction between the sulphonylurea and sulphonamide. You stop the glibenclamide and suggest that he starts glipizide 5 mg twice daily when his blood glucose starts rising. You also suggest they check his blood glucose every 2–3 hours for the next 24 hours (setting the alarm through the night) and making sure that he has extra carbohydrate if he needs it. Careful monitoring is required as patients who get hypoglycaemic on glibenclamide will often get hypoglycaemic on other oral agents.

Sulphonylureas and repaglinide

Hypoglycaemia is the most frequent and serious adverse effect of sulphonylureas.[2] In the UKPDS,[23] 21% of the patients assigned to glibenclamide treatment experienced a hypoglycaemic episode per year and 1.4% of patients experienced a major hypoglycaemic event per year.[23] The lower the HbA_{1C} glucose levels, the higher the risk of hypoglycaemia *(Figure 5)*.[23]

Hypoglycaemia can occur in any person, but particularly in the elderly, in patients with renal or hepatic impairment, and in patients who are receiving interacting drugs *(Tables 3, 4)*.[2] Other risk factors include calorie restriction, polypharmacy, alcohol abuse,[24] or intense or prolonged exercise.[25]

The incidence of hypoglycaemia differs between sulphonylureas mainly due to pharmacokinetic differences.[26] The risk has been found to be highest with glibenclamide in a number of studies, possibly due to its long half life and renally cleared active metabolites.[26-28] As a result it is recommended that glibenclamide be avoided in high risk patients, such as the elderly and those with renal or hepatic impairment.[2] Some evidence suggests that the incidence of hypoglycaemia is lower with glimepiride compared to glibenclamide, but similar to other sulphonylureas; however, further studies are needed.[29,30] Care is still advisable with glimepiride in the elderly and those with renal or hepatic impairment, because it has a long half life and a renally cleared active metabolite.

Repaglinide is a non-sulphonylurea insulin secretagogue agent which is now available on the Australian market. It has a more rapid onset of action and a shorter half life than sulphonylureas and is taken immediately before each meal. The most frequent and serious adverse effect of repaglinide is hypoglycaemia,[2,31] the incidence being only slightly lower than that of the sulphonylureas.[31–33] Because of its rapid onset of action, hypoglycaemia may particularly result if a dose is taken and a meal is delayed or omitted[24] or does not contain adequate carbohydrate.

Patients starting sulphonylureas or repaglinide should be educated about the prevention, symptoms and treatment of hypoglycaemia.

Table 5. Important contraindications to acarbose*[20,37,38]

- Inflammatory bowel disease
- Partial intestinal obstruction (or predisposition)
- Gastrointestinal disorders associated with malabsorption
- Conditions aggravated by formation of intestinal gas (eg. hernias)

* Acarbose is also considered contraindicated in patients with severe renal impairment.[18,20,37]

Table 6. Important contraindications to the glitazones

- Severe heart failure (NYHA Class III or IV)*
- Moderate to severe liver impairment and where ALT > 2.5 times the upper limit of normal at the start of treatment

* New York Heart Association (NYHA) Class III = marked limitation of physical activity which interferes with work; walking on the flat produces symptoms; NYHA Class IV — unable to carry out any physical activity without symptoms; breathless at rest.

Case 3 — Neville

'The tablets you gave me for my diabetes really gave me the trots.' You had prescribed acarbose 50 mg tablets suggesting Neville start with one tablet twice daily and increase to two tablets twice daily because Neville's newly diagnosed type 2 diabetes had not responded adequately to the minor lifestyle change that seemed appropriate (predominantly increasing activity since he was already careful with his food because of his long standing Crohn's disease).

You had warned him about potential gastrointestinal side effects but are surprised when he tells you how severe they became as he persisted with the acarbose schedule (6–8 bowel actions each day, getting up at night and having perianal excoriation).

Neville's Crohn's disease has been stable on sulphasalazine 1 g twice daily for the last few months and you wonder if there is some drug interaction. There is no mention of this in MIMS and when you call your pharmacist colleague she confirms this from her listing but notes that acarbose might be expected to have more severe adverse gastrointestinal side effects in someone with pre-existing gastrointestinal problems.

Neville had stopped the acarbose anyway and wasn't prepared to try it again so you prescribed glipizide 5 mg tablets starting with one per day.

Acarbose

Acarbose is a reversible competitive inhibitor of the alpha-glucosidase enzymes in the brush border of the small intestine that break down dietary carbohydrate.[36,37] Acarbose therefore reduces the rate of glucose production and absorption and results in a more even distribution of glucose absorption throughout the small and large intestine. As a result of its mechanism of action, adverse effects such as flatulence, diarrhoea and abdominal pain are common due to increased gas formation from fermentation of unabsorbed carbohydrates in the colon.[2,38]

Gastrointestinal adverse effects may be reduced by initiation with low doses and very gradual dose titration.[2] Gastrointestinal tolerability usually improves after 4–8 weeks.[36] The risk of gastrointestinal adverse effects is increased in patients also taking metformin.

Because of the high incidence of such adverse effects acarbose is considered contraindicated in patients with the conditions outlined in *Table 5.*

Acarbose does not cause hypoglycaemia but can do so when used in combination with sulphonylurea. In this setting hypoglycaemia should be treated with glucose rather than sucrose as acarbose will prevent metabolism of sucrose.

Case 4 — Hazel

'Do I have to?'

Hazel is very reluctant to start insulin despite taking seven tablets a day for her diabetes (gliclazide 160 mg twice daily, metformin 500 mg twice daily, pioglitazone 45 mg/day). However, her glycaemic control is well outside target (HbA_{1C} 9.8%; target < 7%). She also has symptoms that interfere with her life: 'terrible' thrush, nocturia, lethargy and postprandial sleepiness. You are reluctant to increase her metformin because of her heart failure and renal impairment (plasma creatinine 0.14 mmol/L).*

Despite her age (74) and medical problems Hazel enjoys life. She no longer plays bowls 'because it is too far between ends' and she gets breathless but she manages to look after herself, her unit and a small garden.

Apart from her hypoglycaemic medication she takes digoxin 0.125 mg/day, perindopril 2 mg/day, frusemide 40 mg at breakfast and lunch and a night time isosorbide nitrate patch (to reduce shortness of breath at night). When her arthritis plays up she takes slow release

paracetamol and hasn't needed steroids for some months.

After some discussion she reluctantly agrees and you refer her to the Diabetes Centre to learn how to use an insulin pen. She weighs 60 kg and since she is not overweight† you calculate her daily insulin requirement to be approximately 30 units (50% of her lean weight). You prescribe a bit less to minimise the risk of hypoglycaemia and a twice daily schedule of intermediate insulin at breakfast and the evening meal (16 and 8 units respectively).

One night a fortnight later she becomes very short of breath and is taken to hospital where her pulmonary oedema is successfully treated. A discharge letter comments that the treating doctors had stopped her pioglitazone and metformin because of her impaired cardiac and renal function and have increased her morning and evening insulin doses (to 24 and 12 units respectively).

Glitazones (rosiglitazone and pioglitazone)

Rosiglitazone and pioglitazone are insulin-sensitising agents that heighten the response to insulin in adipose tissue, skeletal muscle and the liver, without stimulating insulin secretion.[39–41] While they are not currently subsidised through the PBS they are being initiated in hospital settings and are available on private prescription.

There are two main contraindications to the glitazones, as outlined in *Table 6.* It is important to avoid the glitazones in patients with severe heart failure as fluid retention, blood plasma volume expansion and oedema are common adverse effects of these drugs.[42] The reported incidence of oedema is 3–5%[41,42] and is highest when glitazones are combined with insulin.[41,43]

Because of reports of rare but sometimes lethal hepatic toxicity, the first of the glitazone class, troglitazone was voluntarily withdrawn from the market in Australia in April 2000. The incidence of hepatic injury with rosiglitazone and pioglitazone appears to be less than that seen with troglitazone. In clinical trials, for example, the incidence of ALT elevation > three times the upper limit of normal was 0.25% with rosiglitazone, 0.26% with pioglitazone and 0.25% with placebo (compared with 1.9% with troglitazone).[44]

Up to February 2002, ADRAC had received eight reports of hepatic adverse effects possibly associated with rosiglitazone and two with pioglitazone. Further information is required to determine the risk of hepatic adverse effects with rosiglitazone and pioglitazone.

Because of concerns about potential hepatotoxicity, glitazones should be avoided in patients with moderate to severe liver impairment and where ALT > 2.5 times the upper limit of normal at the start of treatment.[34,50]

Regular monitoring of liver function tests is needed in patients taking these drugs. The drug should be discontinued if ALT increases to three times the upper limit of normal during therapy and remains elevated, or if jaundice develops.[47, 48, 52]

* Calculated GFR = (140 minus age) x ideal weight ÷ (plasma creatinine x 1000) = (140–74) x 60 ÷ 140 = 28 mL/min.

† She was 1.64m tall and her BMI was therefore 60 ÷ 1.642 = 22.3kg/m2

References:

1. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352(9131): 854–865.
2. Rossi S, Hurley E, Vitry A, et al. (Eds.) Australian Medicines Handbook. 2nd ed. Adelaide: Australian Medicines Handbook Pty Ltd. 2000.
3. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 1999; 131(4): 281–303.
4. Melchior WR, Jaber LA. Metformin: an antihyperglycemic agent for treatment of type II diabetes. Ann Pharmacother 1996; 30(2): 158–164.
5. Howlett HC, Bailey CJ. A risk–benefit assessment of metformin in type 2 diabetes mellitus. Drug Saf 1999; 20(6): 489–503.
6. Brady WJ, Carter CT. Metformin overdose. Am J Emerg. Med 1997; 15(1): 107–108.
7. Wildasin EM, Skaar DJ, Kirchain WR, Hulse M. Metformin, a promising oral antihyperglycemic for the treatment of noninsulin–dependent diabetes mellitus. Pharmacotherapy 1997; 17(1): 62–73.
8. Klepser TB, Kelly MW. Metformin hydrochloride: An antihyperglycemic agent. Am J Health Syst Pharm 1997; 54: 893–903.
9. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. Am J Med 1997; 102(1): 99–110.
10. Lee AJ. Metformin in noninsulin–dependent diabetes mellitus. Pharmacotherapy 1996; 16(3): 327–351.
11. Lim PS, Huang CC, Wei JS. Metformin–induced lactic acidosis: report of a case. J Formos. Med Assoc. 1992; 91(3): 374–376.
12. Pearlman BL, Fenves AZ, Emmett M. Metformin–associated lactic acidosis. Am J Med 1996; 101(1): 109–110.
13. Jurovich MR, Wooldridge JD, Force RW. Metformin–associated nonketotic metabolic acidosis. Ann Pharmacother 1997; 31(1): 53–55.
14. Safadi R, Dranitzki–Elhalel M, Popovtzer M, Ben Yehuda A. Metformin–induced lactic acidosis associated with acute renal failure. Am J Nephrol. 1996; 16(6): 520–522.
15. Victorian Drug Usage Advisory Committee. Therapeutic Guidelines: Endocrinology. 2nd ed. Nth Melbourne: Therapeutic Guidelines Limited, 2001.
16. Gilbert RE, Cooper ME, Krum H. Drug administration in patients with diabetes mellitus. Safety considerations. Drug Saf 1998; 18(6): 441–455.
17. Lalau JD, Vermersch A, Hary L, Andrejak M, Isnard F, Quichaud J. Type 2 diabetes in the elderly: an assessment of metformin (metformin in the elderly). Int J Clin Pharmacol. Ther. Toxicol. 1990; 28(8): 329–332.
18. Charpentier G, Riveline JP, Varroud–Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. Diabetes Metab 2000; 26 Suppl 4: 73–85.
19. Hulisz DT, Bonfiglio MF, Murray RD. Metformin–associated lactic acidosis. J Am Board Fam. Pract. 1998; 11(3): 233–236.
20. Caswell A, Jarvis V, Dalton C, Gagic V. (Eds.) 2000 MIMS Annual. 24th ed. St Leonards NSW: Havas MediMedia, 2000.
21. Chan NN, Brain HP, Feher MD. Metformin–associated lactic acidosis: a rare or very rare clinical entity? Diabet Med 1999; 16(4): 273–281.
22. Hart SP, Walker JD. Is metformin contra–indicated in diabetic patients with chronic stable heart failure? Practical Diabetes International 1996; 13(1):18–20.

23. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood–glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352(9131): 837–853.
24. Luna B, Hughes AT, Feinglos MN. The use of insulin secretagogues in the treatment of type 2 diabetes. Prim. Care 1999; 26(4): 895–915.
25. Benz J, Jackson JE, Pietrusko RG, Ruck B, Mutschler E. Drugdex(R) Editorial Staff. Glyburide. Micromedex Inc. 2001; 108.
26. Harrower ADB. Comparative tolerability of sulphonylureas in diabetes mellitus. Drug Saf 2000; 22(4): 313–320.
27. van Staa T, Abenhaim L, Monette J. Rates of hypoglycemia in users of sulfonylureas. J Clin. Epidemiol 1997; 50(6): 735–741.
28. Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in Type 2 diabetic patients treated with long–acting versus short– acting sulphonylureas. Diabet. Med 1999; 16(7): 586–590.
29. Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. Drugs 1998; 55(4): 563–584.
30. Anon. Amaryl – Generic Name: Glimepiride. Curr Ther 2001; 42(3): 99–101.
31. Guay DR. Repaglinide, a novel, short–acting hypoglycemic agent for type 2 diabetes mellitus. Pharmacotherapy 1998; 18(6): 1195–1204.
32. Schatz H. Preclinical and clinical studies on safety and tolerability of repaglinide. Exp. Clin. Endocrinol. Diabetes 1999; 107(Suppl 4): S144–S148.
33. Kristensen JS, Frandsen KB, Bayer T, Muller P. Repaglinide treatment is associated with significantly less severe hypoglycaemic events compared to sulphonylureas (Abstract). Diabetologia 1999; 42(Suppl 1): A4.
34. Caswell A, Jarvis V, Dalton C, Gagic V, editors. MIMS Supplement No. 3 2000 Annual. St Leonards NSW: Havas Medimedia, 2000.
35. Shenfield, G. Australian Diabetes Society Newsletter. November 2001.
36. Campbell LK, White JR, Campbell RK. Acarbose: Its role in the treatment of diabetes mellitus. Ann Pharmacother 1996; 30: 1255–1262.
37. Yee HS, Fong NT. A review of the safety and efficacy of acarbose in diabetes mellitus. Pharmacotherapy 1996; 16(5): 792–805.
38. Martin AE, Montgomery PA. Acarbose: An alpha–glucosidase inhibitor. Am J Health Syst Pharm 1996; 53: 2277–2290.
39. Adis editors. Avandia. Generic name: rosiglitazone. Curr Ther 2000; 41(10): 83–85.
40. Malinowski JM, Bolesta S. Rosiglitazone in the treatment of type 2 diabetes mellitus: a critical review. Clin Ther 2000; 22(10): 1151–1168.
41. Gillies PS, Dunn CJ. Pioglitazone. Drugs 2000; 60(2): 333–343.
42. Daniel K. The glitazones: proceed with caution. West J Med 2000; 173(1): 54–57.
43. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin–treated type 2 diabetes. Diabet Car 2001; 24(7): 1226–1232.
44. Tolman KG. Thiazolidinedione hepatotoxicity: a class effect? Int J Clin Prac 2000; Suppl 113: 29–34.
45. Hachey DM, O'Neil MP, Force RW. Isolated elevation of alkaline phosphatase level associated with rosiglitazone. Ann Intern Med 2000; 133(9): 752.
46. Al Salman J, Arjomand H, Kemp DG, Mittal M. Hepatocellular injury in a patient receiving rosiglitazone. A case report. Ann Intern Med 2000; 132(2): 121–124.
47. Ravinuthala RS, Nori U. Rosiglitazone toxicity. Ann Intern Med 2000; 133(8): 658.
48. Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. Ann Intern Med 2000; 132(2): 118–121.
49. Maeda K. Hepatocellular injury in a patient receiving pioglitazone. Ann Intern Med 2001; 135(4): 306–306.
50. Eli Lilly Australia Pty.Limited. Product information. Actos (pioglitazone hydrochloride). 2001. Eli Lilly Australia.
51. New drug overview. Pioglitazone hydrochloride. Am J Health Syst Pharm 2000; 57(2): 124–125.
52. McEvoy GK, Litvak K, Welsh OH, Snow EK, editors. American Hospital Formulary Service 2000. Bethesda, MD: American Society of Health–System Pharmacists, 2000.

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