

OVERVIEW OF THE ANTIDIABETIC AGENTS

SPRING 2003

JACK DeRUITER

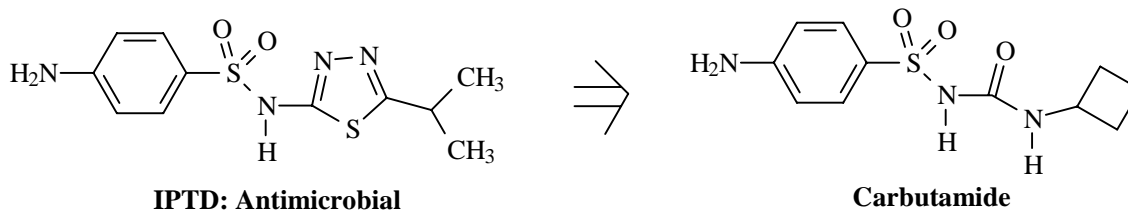
***ORAL HYPOGLYCEMICS/ANTIDIABETICS:
LEARNING OBJECTIVES***

Jack DeRuiter

- Structural classification (i.e. sulfonylurea) and sub-classification (i.e. generation)
- Key structural features that contribute to pharmacologic/therapeutic profile and differences in activity within a structural subclass (i.e. sulfonylureas)
- Detailed understanding of the mechanism of action for each drug/drug class.
 - Pancreatic and/or extra-pancreatic mechanism(s)?
 - Insulin dependent or independent action
 - Compare drugs from different structural classes in terms of mechanism
- Relative potency and efficacy within a structural series (sulfonylureas) and across series. Also efficacy of monotherapy versus combinations
- Indications: Generally as adjuncts to diet/exercise
 - Monotherapy
 - Combination therapy with other oral hypoglycemics, insulin, etc.
- Factors influencing bioavailability (food, drugs, first pass)
- Key disposition factors (protein binding in sulfonylureas)
- Relative onset of action and relationship to mechanism or other factors
- Relative duration of action and factors that influence duration of action
- Metabolic processes and activity of metabolites (contribution to therapeutic activity)
- Elimination profile: Renal and/or non-renal as parent drug and/or metabolites?
- Use/cautions in renally or hepatically impaired patients
- Adverse reactions:
 - Relative incidence of hypoglycemia and relationship to mechanism of action, duration of action, etc.
 - Weight gain
 - GI effects (especially biguanides and acarbose, etc.)
 - Effects on renal physiology (diuresis, fluid retention, etc.)
 - Other key agents: i.e. lactic acidosis (biguanides)
 - Similarities and differences within a series (sulfonylureas) and between structural series in key adverse reactions
- Significant drug interactions that may compromise efficacy:
 - Pharmacokinetic-based interactions: Interference with absorption, Metabolism/Cytochrome-based interactions, Competition for elimination, etc.
 - Pharmacologic: Use with other drugs with hypoglycemic or hyperglycemic actions.
 - Similarities and differences within a series (sulfonylureas) and between structural series for key drug interactions:

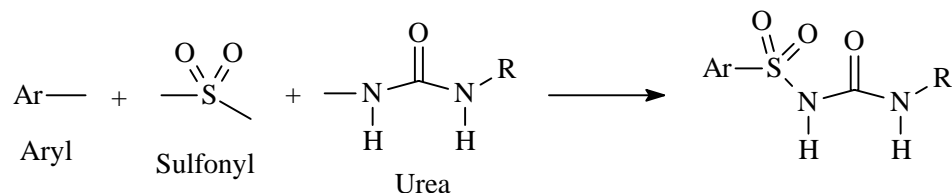
**DRUGS THAT ALTER INSULIN ACTION:
THE SULFONYLUREA ORAL HYPOGLYCEMIC AGENTS**

I. Introduction/Development:

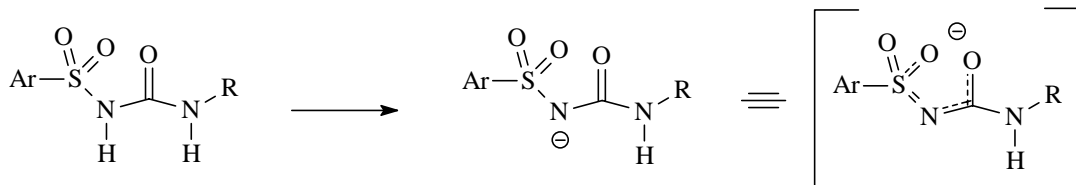


II. Structure and Properties of Hypoglycemic Sulfonylureas

- General structure



- The Ar and R portions of this general structure provide **lipophilic** character whereas the -SO₂-NH-CO-NH- moiety is **hydrophilic**. All of these functional groups are required for activity, but the lipophilic Ar and R groups account for the differences in **potency (SU receptor binding), metabolism, duration, and routes of elimination**.
- The arylsulfonylureas are weak organic acids (pK_as = 5-6) and are largely ionized at physiological pH. This ionization contributes significantly to drug potency SUR (affinity), extensive plasma protein binding of these agents (>95%), and drug interactions (competitive ppb). Also, alkalization of the urine enhances ionization and elimination (shortens half-life!).



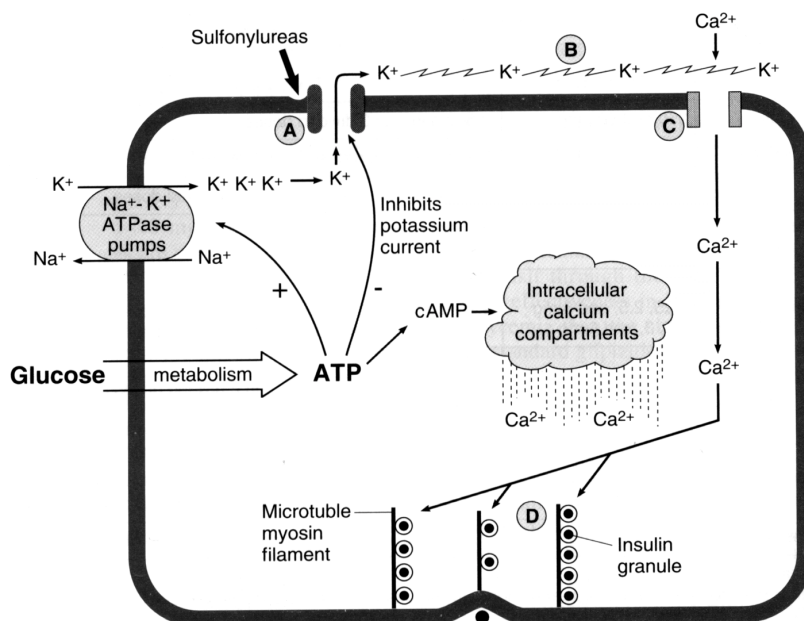
- The arylsulfonylureas products differ primarily in their relative **potency** and key **pharmacokinetic** properties. **Duration of action** (primarily a function of metabolism) is of primary importance because this influences the frequency of required dosing (see Table later).
- The sulfonylureas can be classified as **first, second and possibly third** generation agents. The 2nd and 3rd generation sulfonylurea hypoglycemics (glipizide, glyburide and glimepiride) are the newer, “more potent” agents.

III. Pharmacologic Properties and Therapeutic Uses

- Oral hypoglycemic agents are commonly prescribed drugs that find utility in controlling the symptoms of diabetes in the ~80% of patients having NIDDM. Since **insulin resistance** and **impaired insulin secretion** are key factors in the pathogenesis of NIDDM, treatment should be directed toward restoring metabolic normality by improving insulin secretion and reducing insulin resistance. These goals are accomplished through the use of oral hypoglycemic agents, specifically the **sulfonylureas**.
- **Mechanism(s) of Sulfonylurea Hypoglycemia.**

The sulfonylureas produce their hypoglycemic actions via several mechanisms that can be broadly sub-classified as **pancreatic** and **extra-pancreatic**:

A. Pancreatic Mechanism: All sulfonylurea hypoglycemics inhibit the efflux of K^+ (K^+ channel blockers) from pancreatic β -cells via a sulfonylurea receptor which may be closely linked to an ATP-sensitive K^+ -channel. The inhibition of efflux of K^+ leads to depolarization of the β -cell membrane and, as a consequence, voltage-dependent Ca^{++} -channels on the β -cell membrane then open to permit entry of Ca^{++} . The resultant increased binding of Ca^{++} to calmodulin results in activation of kinases associated with endocrine secretory granules thereby promoting the exocytosis of insulin-containing secretory granules:



B. Extra-Pancreatic Mechanisms:

- The sulfonylureas also reduce serum glucagon levels possibly contributing to its hypoglycemic effects. The precise mechanism by which this occurs remains unclear but may result from indirect (secondary) inhibition due to enhanced release of both somatostatin and insulin.
- Sulfonylureas may also potentiate insulin action at target tissues (drug-dependent characteristic).

Endocrine Pharmacotherapy Module, Spring, 2003

	FIRST GENERATION SULFONYLUREAS				SECOND GEN. SULFONYLUREAS		
PROPERTY	TOLBUTA.	ACETOHEX.	TOLAZAM.	CHLORPR.	GLIPIZIDE	GLYBUR.	GLIMEP.
Relative potency	1	2.5	5	6	100	150	>150
Equivalent Therapeutic dose (mg)	1000-1500	500-750	250-375	250-375	5-10	3-5	2
Duration (hr)	6-12	12-24	12-24	24-72	10-24	16-24	18-28
# Doses/day	2-3	2	1-2	1	1-2	1-2	1
% PPB	95-97	65-88	94	88-96	92-97	99	99
SerumT _{1/2} (hr)	4.5-6.5	6-8	7	36	2-4	10	9
Urinary excretion products (% of dose)	p-Carboxy (60)§ p-HOCH ₂ (30)* Other (8) Parent (2)	HOAHX (65)† 4-OH (15)§ Di-OH (18)§ Parent (2)	Carboxy (17)§ p-HOCH ₂ (35)‡ Other (31) Parent (7)	Parent (20) 2-OH (55)* 3-OH (2)* Other (4)	Parent (3) 3-OH (15)* 4-OH (60)* Other (10)	Parent (3) 3-OH (9)§ 4-OH (36)‡ Other (2)	HOCH ₂ (M1) COOH (M2)
Fecal excretion	Negligible	Negligible	Negligible	Negligible	15%	50%	40%
Diuretic	Yes	Yes	Yes	No	Weak	Yes	No
Antidiuretic	Yes	No	No	Yes	No	No	No
Dosage Adjust	No						
In renal imp							

*= Weakly active, † = more active than parent, ‡ = Moderately active, § = Inactive

Generally, the 2nd generation agents are no more efficacious than the 1st generation agents even though they are “more potent”. The potency difference is reflected primarily in the differences in dose. Also, some reports suggest the newer generation agents may have a lower incidence of some adverse reactions, due to the lower doses used.

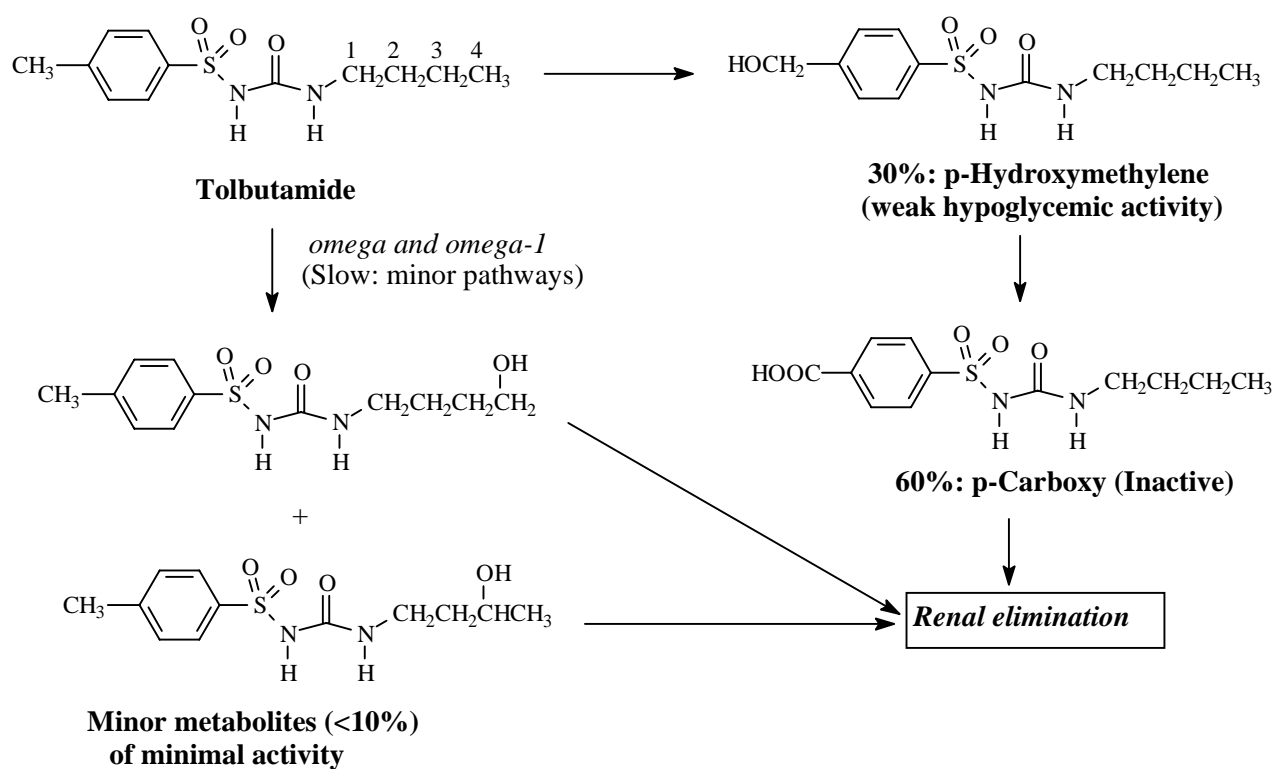
IV. Pharmacokinetic Properties

The table on the preceding page (page 5) compares several properties of orally administered sulfonylurea hypoglycemic agents. These parameters are discussed in more detail in the sections that follow:

V. Properties of the Sulfonylurea Drug Products

A. Tolbutamide (OrinaseTM and generics)

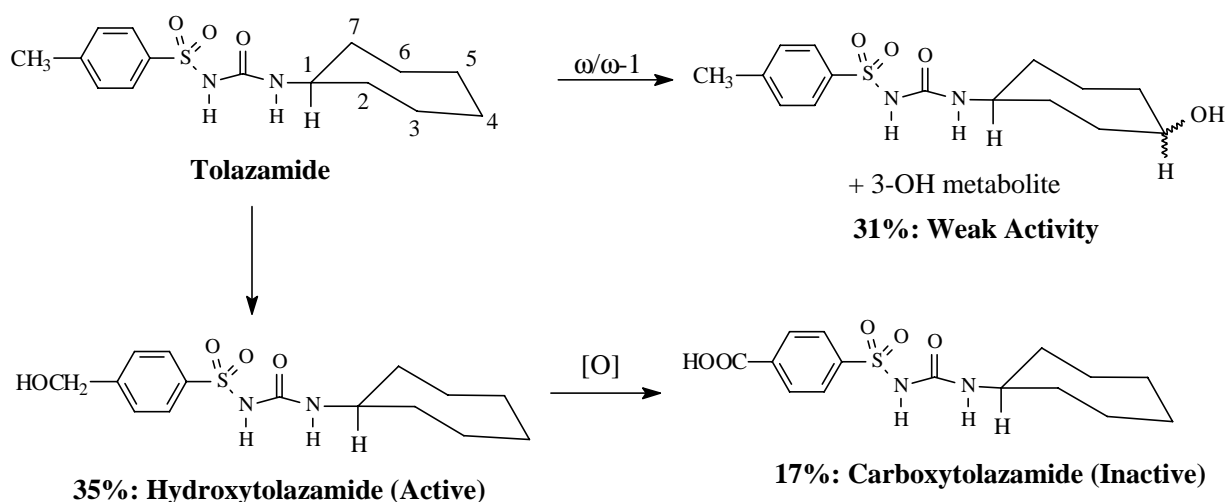
- the **free acid** (oral - rapidly absorbed) and the **sodium salt** (IV).
- IV solutions of the salt form are **unstable** must be administered within an hour. Otherwise significant hydrolysis of the sulfonamide bond may occur.
- the **least potent** oral hypoglycemics: Low SUR receptor affinity
- a relatively **short** duration of action due primarily to rapid metabolic inactivation by oxidative metabolism of the p-methyl (benzylic) group, first to the hydroxymethylene primary alcohol, then to the inactive acid.



- Use Profile: Preferred agent in patients with moderate to severe renal impairment and thus is among the safest sulfonylurea for use **in the elderly and renally impaired**. There are some rare acute adverse reactions (see below).
- Some drug-drug interactions (dicumarol, phenylbutazone, or some sulfonamides) - see below

B. Tolazamide (TolinaseTM and generics)

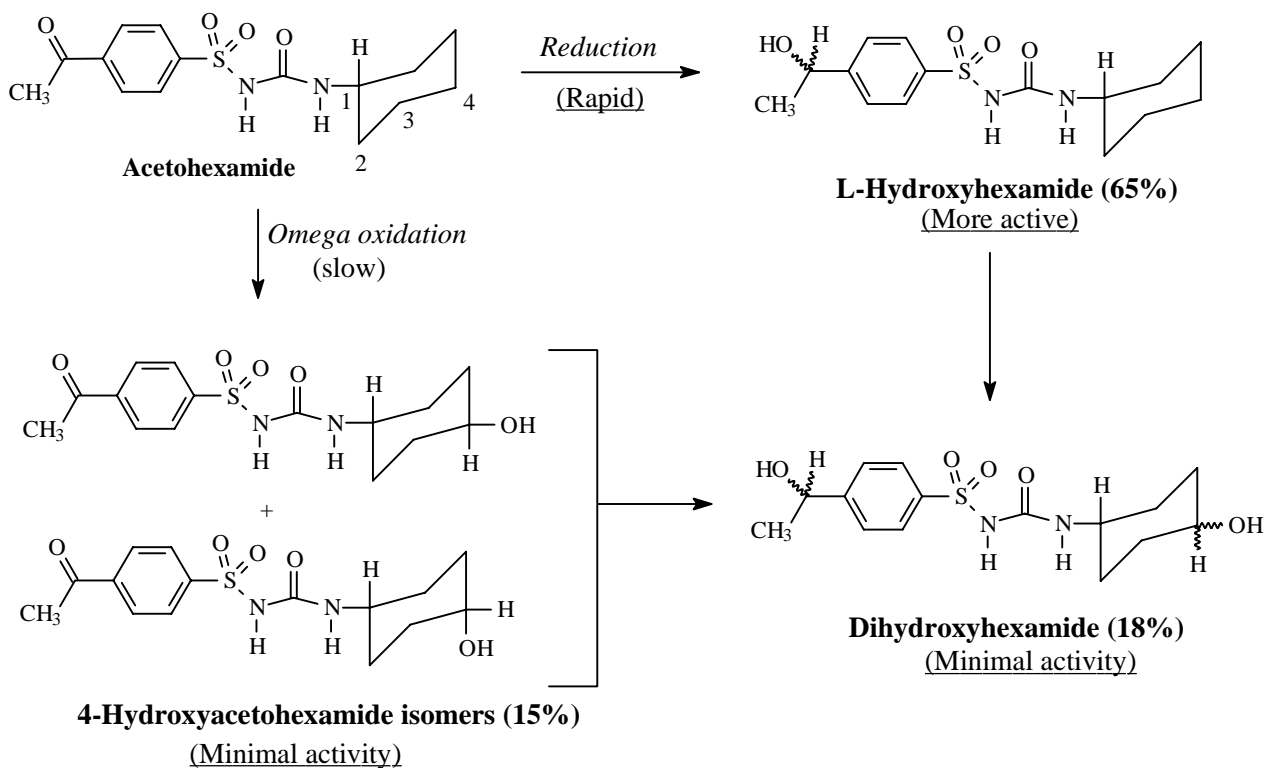
- a cyclic derivative of tolbutamide, that is **more potent** than tolbutamide, roughly equal to chlorpropamide in hypoglycemic activity.
- Longer duration than tolbutamide, shorter than chlorpropamide
- Metabolically inactivated by oxidative pathways, including benzylic oxidation similar tolbutamide. The longer duration of action versus tolbutamide may result from its slower rate of absorption from the GIT and the formation of active hydroxy metabolites; these metabolites are more active than tolbutamide!



- Slow absorption; delayed effect on blood glucose (see kinetics below)
- Careful in renally impaired patients since active metabolite is eliminated renally and may accumulate (risk of hypoglycemia).

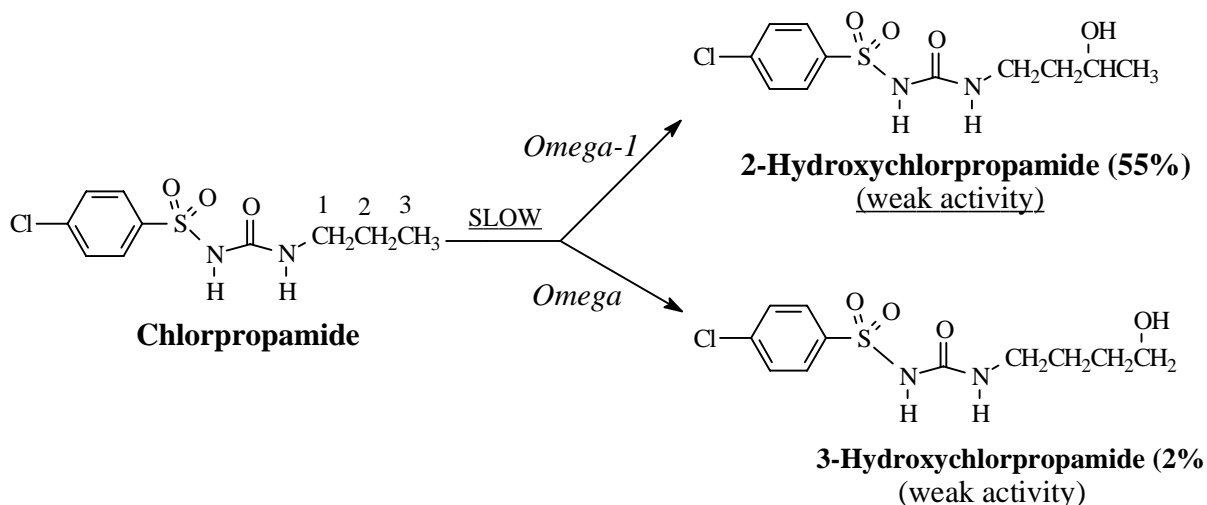
C. Acetohexamide (DymelorTM c)

- Unique structural features include a p-acetyl moiety and a cyclohexyl group on the terminal urea.
- Rapidly metabolized by reduction of the acetyl carbonyl to the L-stereoisomeric alcohol, L-(-)-hydroxyhexamide which is 2.5X as active as the parent drug and has a longer half-life! Acetohexamide and L-(-)-hydroxyhexamide are also metabolized by omega-like oxidation of the cyclohexyl 4-position. The dihydroxy metabolite formed from L-(-)-hydroxyhexamide has lower hypoglycemic activity. Further metabolism results in inactivation.
- It has an intermediate duration (>tolbutamide, < chlorpropamide) as a result of formation of an active L-(-)-hydroxyhexamide metabolite (SEE NEXT PAGE!). Parent and active drug may accumulate in renal impairment!
- Highest risk of hypoglycemic reaction, worst side effect profile, more frequent dosing.
- Parent drug and metabolites have diuretic and potent uricosuric activity.



D. Chlorpropamide (Diabinese™ and generics)

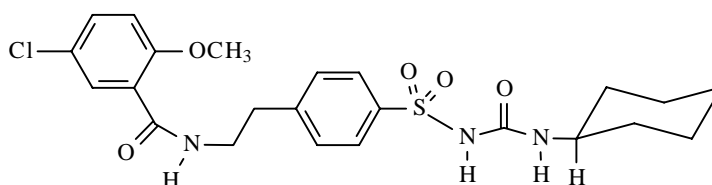
- a **more potent** and **prolonged acting** (mean elimination $t_{1/2}$ 33 hrs) since it is only slowly metabolized in vivo - the **p-Cl substituent** protects the p-position from metabolic oxidation.
- 20% of a dose excreted unchanged (80% metabolism by (ω and ω -1 type oxidation!). Therefore **impaired renal function, as in elderly patients**, can lead to accumulation of the drug and an enhanced hypoglycemic effect (caution!).



- Dilutional hyponatremia -- results from enhanced vasopressin secretion and potentiation of its effect at the renal tubule by rare chlorpropamide hematologic toxicity (SIADH)
- Some drug-drug interactions (dicumarol, phenylbutazone, or some sulfonamides)
- May produce a disulfiram reaction (inhibition of alcohol metabolism) with symptoms including nausea/vomiting, hypotension, breathlessness and flushing.
- Also used in diabetes insipidus

E. Glyburide (Micronase™, Diabeta™ and Glyburide micronized (Glynase™ and generics)

- a so-called **second-generation**, high potency sulfonylurea hypoglycemic; Note more complex structure of the Ar moiety that facilitates receptor binding, and influences excretion profile (see below).

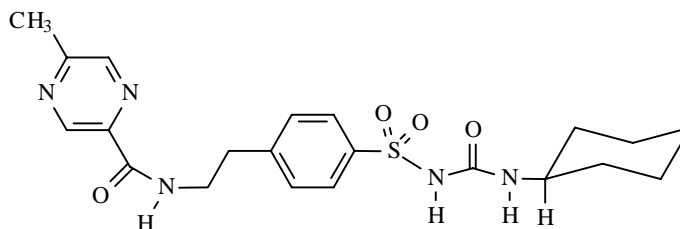


Glyburide

- Onset is about 1.5 hrs. Administer about 30 minutes before meal (breakfast)
- Glyburide is **extensively bound** by plasma proteins and is **recycled** hepatically. Both of these factors contribute to prolonged duration of action. These are also a function of the complex Ar moiety.
- Metabolized in the liver. Glyburide has a **short plasma half-life** (2-10 hrs) but **prolonged biological effect** due to the formation of active metabolites! It is metabolized primarily by oxidation of the cyclohexyl ring (ω and $\omega-1$ type oxidations), of the 4 possible isomeric metabolites, the *cis*-3-OH and *trans*-4-OH compounds are the major ones formed (see metabolism figure on next page).
- Elimination profile: 50% renal and 50% biliary.
- **Other than hypoglycemia**, fewer adverse effects than most first generation agents. It does not cause water retention (as does chlorpropamide). Hypoglycemia may be a problem due to the drug's prolonged therapeutic action.
- Contraindications based on clearance profile: **hepatic impairment** and **renal insufficiency**. Dose reduction is required in the elderly (from 2.5 mg/day to 1.25 mg/day).
- Combination formulations with metformin (Glucovance™) also available (see "Biguanide" section).

F. Glipizide (Glucotrol™ and Glucotrol XL™)

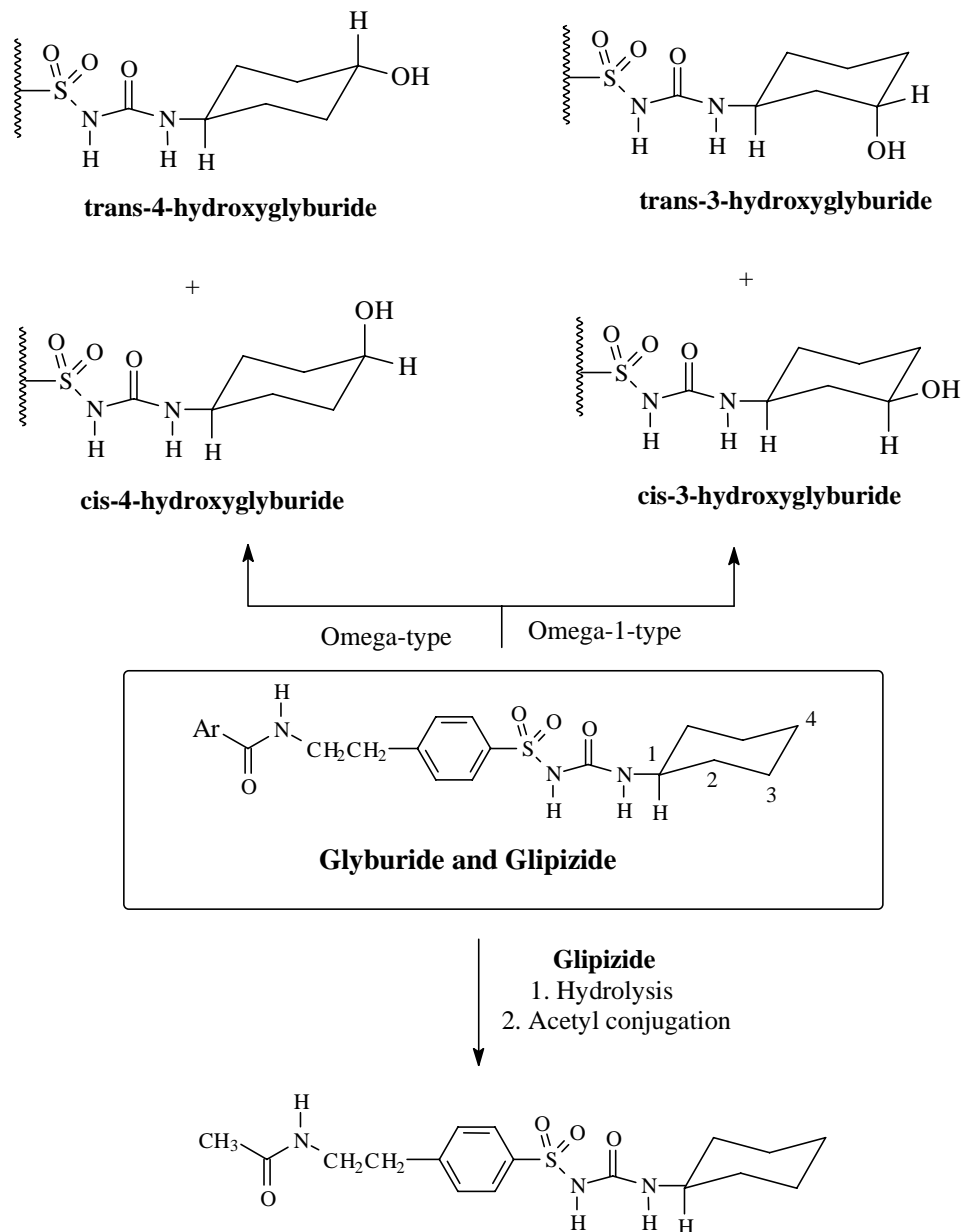
- a high potency, long acting (high plasma protein binding and hepatic recycling) second-generation sulfonylurea, factors again resulting from the Ar moiety present in this compound (like glyburide).



Glipizide

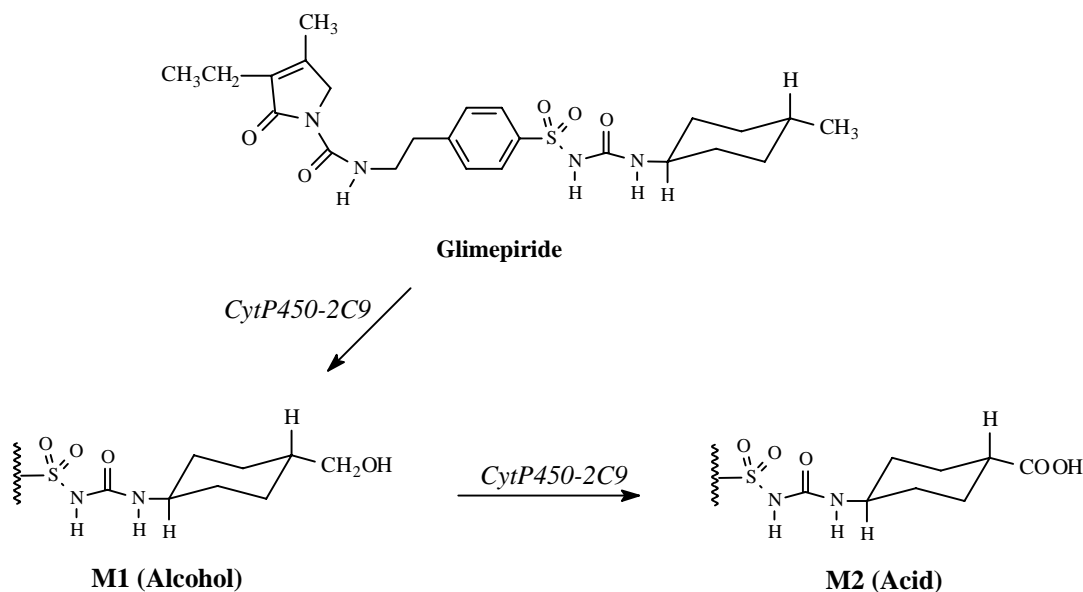
- Absorption rate reduced when taken with meals; take on an empty stomach
- Shortest half-life (2-4 hours) as the parent drug but extended released formulation ("XL") also is available providing 24-hour action. It is extensively metabolized by the liver (90%); 10% excreted unchanged by the kidney. It is metabolized primarily by ring ω and ω -1 oxidations with *cis*-3-OH and *trans*-4-OH predominating. Some hydrolysis of the heterocyclic (electron deficient) amide may also occur (see metabolism figure on next page). The metabolites have relatively of low activity:
- Less likely than glyburide to produce serious hypoglycemia due primarily to its shorter half-life.
- Contraindications based on clearance profile: **hepatic dysfunction** and **renal insufficiency**. Can be used in patients with moderate to severe renal impairment.
- Metabolism profiles of Glipizide and Glyburide. ω and ω -1 type oxidation for 50-75% of the dose as shown below. The 3- and 4-OH metabolites of glipizide have weak hypoglycemic activity. The 3-OH of glyburide has virtually no activity, while the 4-OH has some hypoglycemic activity. Less than 10% of the dose of these drugs undergoes hydrolysis to inactive metabolites.

Metabolism of Glipizide/Glyburide



G. Glimepiride (Amaryl®)

- Glimepiride: is a so-called "third generation" sulfonylurea (see structure below):
- Structural analogue of the second-generation sulfonylureas in which the amide moiety of the 4-arylalkyl substituent has been replaced with a heterocyclic ureido group. This structural modification is reported to result binding to different region of beta cell receptor and in enhanced potency and increased duration. Most potent -- lowest dose of the sulfonylureas
- The primary mechanism of action of glimepiride appears to be the same as other sulfonylureas and involves stimulating the release of insulin from functional pancreatic beta cells. In addition, extrapancreatic effects may also play a role in the pharmacologic action of the sulfonylureas. Classified as third generation.
- Overall, the adverse reaction profile of glimepiride is similar to other sulfonylurea oral hypoglycemics. The incidence of drug-induced hypoglycemia (blood glucose values <60 mg/dL) with glimepiride ranges from 0.9 to 1.7%
- Glimepiride is completely (100%) absorbed upon oral administration (C_{max} at 2-3 hours).
- Protein binding is reported to be greater than 99%.
- Glimepiride is extensively metabolized by hepatic cytochrome enzymes and the major metabolites are the alcohol (M1) and carboxylic acid (M2) formed from sequential oxidation of the cyclohexylmethyl group. The isozyme cytochrome P450 2C9 is involved in the formation of M1. M2 is formed by further oxidation of M1 by one or more cytosolic (non-cytochrome) enzymes. M1 possess about 1/3 the activity of the parent drug (in animal models) while M2 is devoid of hypoglycemic activity. Caution in renal impairment!



- Approximately 60% of the oral dose of glimepiride is eliminated in the urine within 7 days, primarily (80-90% of this fraction) as the M1 (predominant) and M2 metabolites. Approximately 40% is excreted in the feces, again primarily as M1 and M2 (70%). Based on this metabolic and elimination profile, initial dose reduction may be required with renal impairment,
- Long duration of action (18-28 hours) in spite of short plasma half-life = 9 hours

VI. Sulfonylurea Efficacy

- Optimal in patients over 40 yoa, FPG <200 mg/dl, actual weight 110-160% IBW, with duration of disease <5 yrs and no prior treatment with insulin or controlled with <40 units/day insulin.
- Initially 75-90% patients respond. Responding pts show 50-60 mg/dl reductions in FPG and 1-2% reduction in HbA_{1c}.
- Secondary failure rate >10% (variable). Secondary failure may be treated by increasing dose or switching to another sulfonylurea, but these approaches are often not successful (only 10%).
- Sulfonylurea failures due to stress or disease may be treated with temporarily with insulin.

VII. Sulfonylurea Adverse Reactions and Warnings

- Hypoglycemia: Major side effect (function of drug action/dose/duration/patient behavior) and complication of drug therapy. May be more common in the elderly and renally and/or hepatically patients and with more potent, longer acting sulfonylureas (i.e chlorpropamide).
- Weight gain: May be more common with some more potent, longer acting sulfonylureas
- Other ARs: Dermatological (rash, purpura and pruritus), hepatic, GI (N/V and cholestatic jaundice – esp chlorpropamide) and hyperinsulinemia
- Mild diuresis, particularly with tolazamide, acetohexamide and glyburide.
- Fluid retention and hyponatremia with chlorpropamide and, to a lesser extent, tolbutamide
- Use with caution in patients with hepatic dysfunction (metabolism!)
- Use with caution in patients with renal impairment, esp chlorpropamide and also acetohexamide, tolazamide, glyburide and glimepiride!
- Do not use in pregnancy (generally). They cross the placenta. Never use with gestational diabetes.

VI. Sulfonylurea Drug Interactions:

- Because of the importance to regulation of glucose blood levels of maintaining therapeutic plasma levels of the sulfonylureas, pharmacodynamic and pharmacokinetic interactions are of importance:
- A loss of glycemic control may occur when patients are treated concurrently with a sulfonylurea and drugs that produce hyperglycemia. These include thiazides (hydrochlorothiazide, diazoxide), corticosteroids ("adrenal diabetes"), estrogens, oral contraceptives, phenothiazines, thyroid products, phenytoin, nicotinic acid, isoniazid, sympathomimetics, beta-blockers (propranolol) and some calcium channel blockers (nifedipine).
- The hypoglycemic effect of sulfonylureas may be enhanced due to various mechanisms (eg, decreased hepatic metabolism, inhibition of renal excretion, displacement from protein-binding sites, decreased blood glucose, alteration of carbohydrate metabolism). Monitor blood glucose carefully upon initiation, cessation, or changes in therapy with any of these agents:

Androgens	Anticoagulants	Azole antifungals
Chloramphenicol	Clofibrate	Fenfluramine
Fluconazole	Gemfibrozil	Histamine H2 antagonists
Magnesium salts	Methyldopa	MAO inhibitors
Probenecid	Salicylates	Sulfinpyrazone
Sulfonamides	Tricyclics	Urinary acidifiers

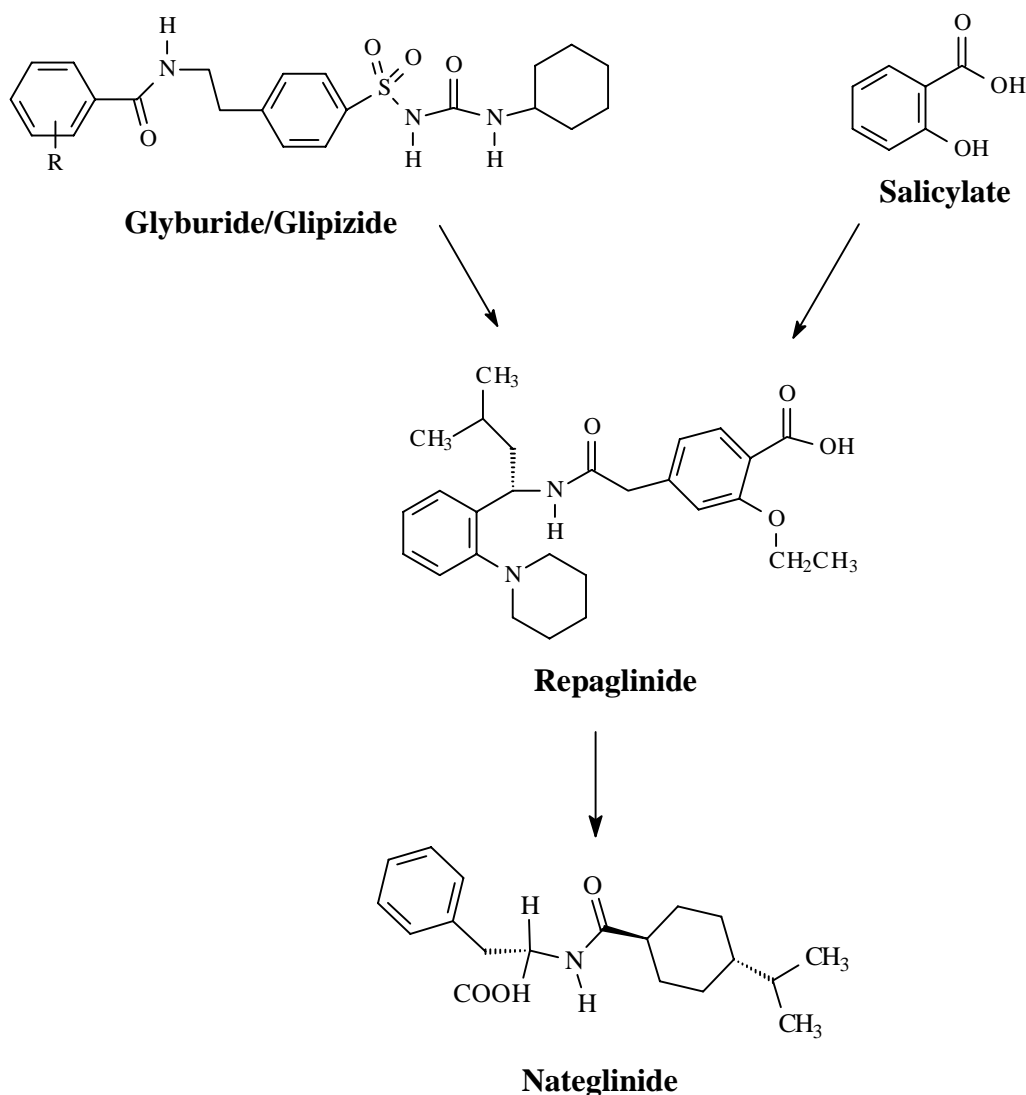
- Drugs that competitively displace sulfonylureas from plasma protein binding sites (other **acidic** drugs such as NSAIDs, sulfonamides, coumarins, probenecid, etc.)
- Also, other drugs are metabolized by cytochrome P450 systems (miconazole, phenytoin, diclofenac, naproxen, mefenamic acid) may decrease clearance of sulfonylureas and precipitate hypoglycemia. Drugs that induce cytochrome enzymes like rifampin, may enhance sulfonylurea clearance and reduce efficacy.
- Table of representative drug interactions:

INTERACTION	DRUG
Displace sulfonylureas from plasma proteins	Clofibrate, phenylbutazone, salicylates, sulfonamides
Reduce hepatic sulfonylurea metabolism	Dicumarol, chloramphenicol, MAOIs, phenylbutazone
Decrease urinary excretion of sulfonylureas or their metabolites	Allopurinol, probenecid, phenylbutazone, salicylates, sulfonamides
Intrinsic hypoglycemic activity	Insulin, alcohol, β -blockers, salicylates, MAOIs, guanethidine

MEGLITINIDES: Repaglinide (Prandin®) and Nateglinide (Starlix®)

I. Development and Pharmacology

- Repaglinide and nateglinide are novel oral blood glucose-lowering agents that are distinct from all other antidiabetic agents in their chemical structure, mechanism of binding to target channels in beta-cells, and mode of elimination. These agents have several desirable properties including a rapid onset and short duration of action and metabolism, and excretion by non-renal routes. Furthermore, they can work synergistically with other antidiabetic drugs such as metformin in patients whose hyperglycemia is not controlled by monotherapy. Thus the meglitinides may offer some advantages in therapy over traditional and even newer antidiabetic drug therapies.
- Repaglinide is a non-sulfonylurea hypoglycemic agent that consists structurally of the non-sulfonylurea moiety of glyburide and a salicylic acid derivative. Both salicylates and sulfonylureas are known to reduce elevated plasma glucose levels, by different mechanisms. Nateglinide is a derivative of the amino acid D-phenylalanine related somewhat to repaglinide.



Mechanistically the meglitinides are similar to the sulfonylureas in they interacts with binding sites on ATP-dependent potassium channels in the beta-cell membrane. These sites are distinct from those involved in sulfonylurea binding. The binding of the meglitinides results in potassium channel blockade which depolarizes the beta cell and leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. Thus the actions of repaglinide are dependent upon functional beta cells in the pancreatic islets. The ion channel binding mechanism of these drugs is highly tissue selective with low affinity for heart and skeletal muscle. Some studies suggest that nateglinide may have a “faster-on/faster-off” action and thus a lesser effect at lower glucose concentrations (less hypoglycemia!).

II. Therapeutics

- Repaglinide is effective in lowering fasting blood glucose concentrations (-31%), glycosylated hemoglobin (0.6-1.0%), 2-hour postprandial plasma glucose (-48%) and mean glucose concentration under the 24 hour blood glucose concentration-time profile. Repaglinide is at least as effective as glyburide and gliclazide, and more effective than glipizide. **Combination therapy with repaglinide and metformin resulted in synergistic improvement in glycemic control compared with either repaglinide or metformin monotherapy.** Mild or moderate hypoglycemia is reported in 16% of the repaglinide patients (1228), 20% of glyburide patients (417) and 19% of glipizide patients.
- Repaglinide Indications: As an adjunct to diet and exercise to lower the blood glucose in patients with type 2 diabetes mellitus whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone. Also may be used in combination with metformin to lower blood glucose in patients whose hyperglycemia cannot be controlled by exercise, diet and either agent alone.
- Nateglinide: Significant reductions in mean HbA1c and mean FPG as monotherapy. **The combination of nateglinide and metformin results in statistically significantly greater reductions in HbA1c and FPG compared with nateglinide or metformin monotherapy.**
- Nateglinide Indications: As monotherapy to lower blood glucose in patients with type 2 diabetes whose hyperglycemia cannot be adequately controlled by diet and physical exercise and who have not been chronically treated with other antidiabetic agents. Also as combination therapy with metformin in patients whose hyperglycemia is inadequately controlled. Nateglinide may be added to, but not substituted for, metformin. Also patients whose hyperglycemia is not adequately controlled with glyburide or other insulin secretagogues should not be switched to nateglinide or have nateglinide added to their treatment regimen.

III. Adverse Reactions

- During comparative clinical trials, 13% of repaglinide patients discontinued therapy because of adverse events vs 14% of sulfonylurea patients. Hypoglycemia and related symptoms were the

most common adverse events resulting in discontinuation, and the incidence of hypoglycemia was slightly lower in the repaglinide versus sulfonylurea treated group. Hypoglycemia was relatively uncommon in all treatment arms of the clinical trials with nateglinide. Only 0.3% of nateglinide patients discontinued because of hypoglycemia.

- It should be noted that with the meglitinides, like other antidiabetic drugs, the risk of serious hypoglycemia may be increased in elderly, debilitated or malnourished patients, and those with adrenal, pituitary or hepatic insufficiency. In general, the adverse reaction profile of repaglinide is similar to that noted for the sulfonylurea drugs, including **weight** gain (5 lb).
- In comparative trials, the incidence of individual cardiovascular adverse reactions (hypertension, abnormal ECG, MI, arrhythmias, palpitations) with meglitinides was not greater than that observed for the sulfonylurea. There also was no increase in frequency or severity of hypoglycemia in older subjects.

IV. Drug Interactions

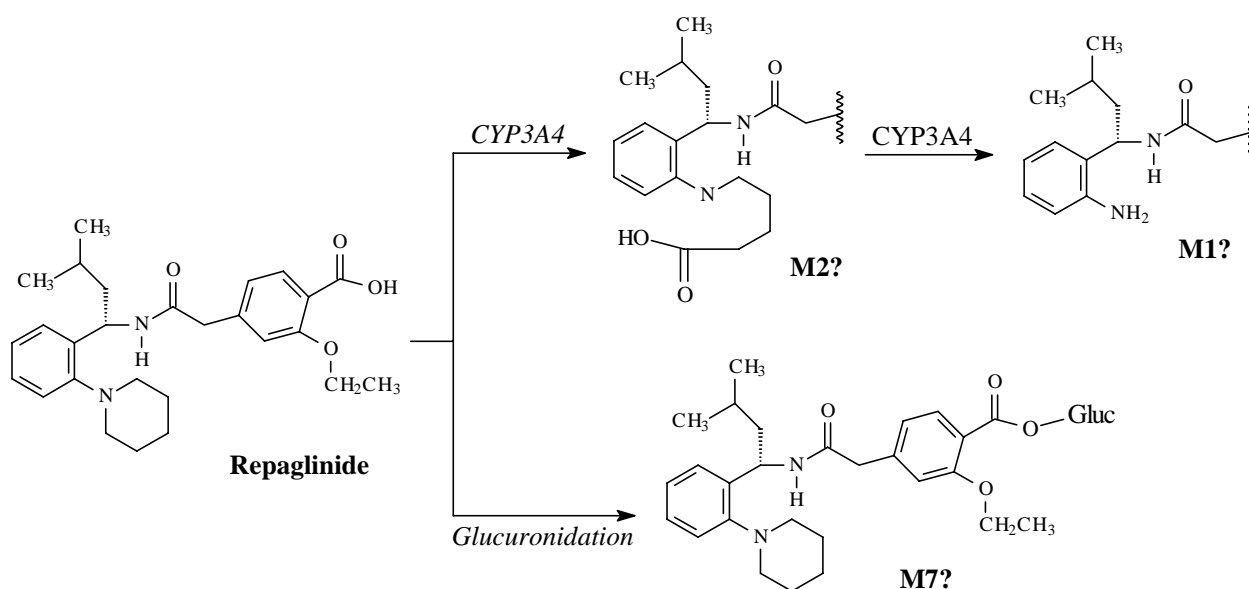
- Currently no clinically significant drug interactions have been reported with repaglinide. However, repaglinide metabolism may be decreased by inhibitors of CYP 3A4 such as the azole antifungal (ketoconazole, miconazole, etc.) and some antibiotics including erythromycin, resulting in increased serum concentrations. Conversely, drugs that induce the CYP 3A4 (i.e. troglitazone, rifampin, barbiturates, carbamazepine) may increase repaglinide metabolism and thereby decrease its antidiabetic the effects when used concurrently.
- In vitro metabolism studies indicate that nateglinide is predominantly metabolized by the cytochrome P450 isozyme CYP2C9 (70%) and to a lesser extent CYP3A4 (30%). Nateglinide is a potential inhibitor of the CYP2C9 isoenzyme in vivo as indicated by its ability to inhibit the in vitro metabolism of tolbutamide. Inhibition of CYP3A4 metabolic reactions was not detected in in vitro experiments.
- The actions of oral hypoglycemic agents may be potentiated by certain drugs including NSAIDs and other drugs that are highly protein bound such as salicylates, sulfonamides, chloramphenicol, coumarins, probenecid, MAOIs, etc. (for a complete listing, see Drug Interactions under Sulfonylureas). Thus patients should be monitored closely for loss of glycemic control when these agents are added to or withdrawn from patients on repaglinide therapy.
- Thiazide diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, isoniazid and other drugs that produce hyperglycemia should be used cautiously and with monitoring in patients treated with repaglinide.

V. Pharmacokinetics

Parameter	Repaglinide	Nateglinide
Oral Bioavailability (%)	56%	73%
Food Effect	Reduced C _{max} (20%) Reduced AUC (12%)	No effect on AUC Reduced C _{max}
T_{max}	≈ 1 hr	≈ 1 hr
Plasma T_{1/2}	≈ 1 hr	
%PPB	>98%	98%
V_d (L)	31	10
Clearance (L/hr)	38	
Metabolism	M2 (OND by CYP3A4) M1 M7	Hydroxylation (2C9 + 3A4) Glucuronidation
Renal Elimination	8%	83%
Fecal Elimination	≈ 90% (mainly M2)	10%
Impaired Hepatic Function	Caution (incr dose interval)	Caution

- Absorption:** Both meglitinides are rapidly absorbed upon oral administration, producing peak plasma levels within an hour. The bioavailability of both drugs appears to be reduced, in part, by modest first pass metabolism. When repaglinide is given with food, the mean T_{max} is not altered, but the mean C_{max} and AUC are decreased by 20% and 12.4%, respectively. But food administration may reduce the risk of hypoglycemia! While the repaglinide AUC ranges 15% to 70% higher in females with type 2 diabetes, this difference does not appear to be reflected in the frequency of hypoglycemic episodes or other adverse events and thus no change in general dosage recommendation appears indicated. When given with or after meals, the extent of nateglinide absorption (AUC) remains unaffected. However, there is a delay in the rate of absorption characterized by a decrease in C_{max} and a delay in the time to peak plasma concentration.
- Distribution:** The volume of distribution for repaglinide at steady state is 31 L, and the total body clearance is 38 L/hr. Protein binding and binding to human serum albumin is estimated at > 98%. Repaglinide is rapidly eliminated from the blood with a half-life of approximately 1 hour. The steady-state volume of distribution of nateglinide is estimated to be » 10 L in healthy subjects. Nateglinide is extensively bound (98%) to serum proteins, primarily serum albumin, and to a lesser extent to acid glycoprotein. The extent of serum protein binding is independent of drug concentration over the test range of 0.1 to 10 mcg/mL
- Metabolism:** Repaglinide is completely metabolized by **oxidative biotransformation and direct conjugation** with glucuronic acid. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1) and the acyl glucuronide (M7). The cytochrome P450 isozyme CYP3A4, is involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. None of these metabolites appear to possess significant antidiabetic activity.

Nateglinide is metabolized by the mixed-function oxidase system prior to elimination. The major routes of metabolism are hydroxylation followed by glucuronide conjugation. The major metabolites are less potent antidiabetic agents than nateglinide. The isoprene minor metabolite possesses potency similar to that of the parent compound nateglinide. In vitro data demonstrate that nateglinide is predominantly metabolized by cytochrome P450 isoenzymes CYP2C9 (70%) and CYP3A4 (30%). Based on this clearance profile, this drug should be used with caution in patients with **chronic liver disease**.



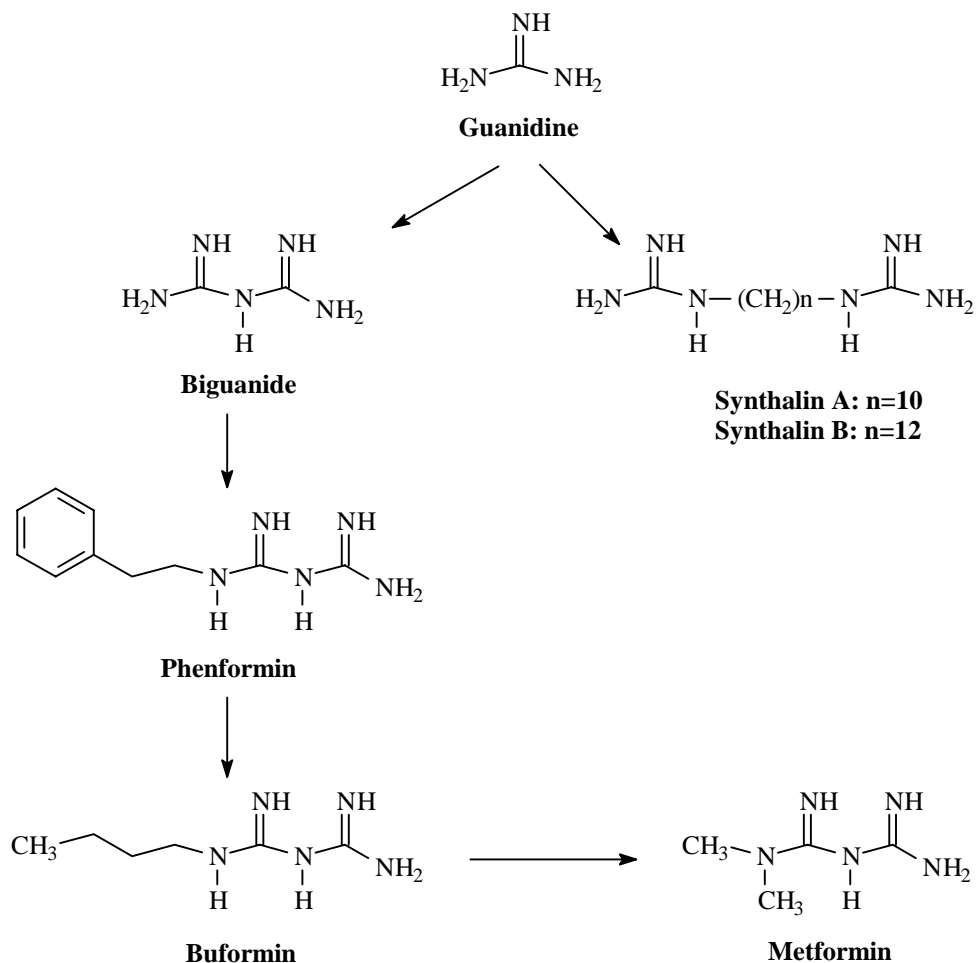
- Excretion:** About 90% repaglinide is recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound and less than 2% of the parent drug is eliminated in the feces. The major metabolite M2 accounts for 60% of the administered dose. Both AUC and C_{max} are reported to be higher in patients with reduced renal function. While initial dosage adjustment does not appear to be necessary in the renally impaired, subsequent dose increases should be done with caution in these patients. Patients with impaired liver function may be exposed to higher concentrations of repaglinide and its metabolites than those with normal liver function receiving usual doses. Therefore, this drug should be used cautiously in these patients and longer intervals between dose adjustments allowed to accurately assess response.

Nateglinide and its metabolites are rapidly and completely eliminated following oral administration. Eighty-three percent is excreted in the urine (mainly as metabolites) with an additional 10% eliminated in the feces. Consistent with this short elimination half-life, there was no apparent accumulation of nateglinide upon multiple dosing. Dose adjustment typically not required in the elderly with either meglitinide.

Biguanides: Metformin (Glucophage®)

I. Development:

- Guanidine found to lower blood glucose in animals in 1918, but too toxic.
- Alkyl-diguanides synthalin A and B were introduced into diabetes therapy in 1920s. Displayed efficacy comparable to insulin, but renal and hepatic damage resulted upon prolonged administration. Discontinued in the 1930s



- The biguanides metformin (dimethylguanide), phenformin (phenylethylbiguanide) and buformin were introduced into clinical practice in 1950s as oral antihyperglycemics for the treatment of non-insulin dependent diabetes mellitus (NIDDM). Phenformin was initially regarded as the most potent biguanide and was used more extensively until its withdrawal in most countries by 1977. **This withdrawal was prompted largely by the association of phenformin therapy with lactic acidosis (rare, but potentially fatal).** Also in the UGDP study the rate of cardiovascular mortality of the phenformin treatment group exceed that of all other treatment groups (validity of the study?).

- Metformin has not been linked with a significant incidence of lactic acidosis, thus it continued to be used in approximately 90 countries for the management of NIDDM that is not adequately controlled by diet alone. Lactic acidosis rate reported to be 0.084/1000 for metformin versus 0.25 to 4/1000 with phenformin. Incidence of lactic acidosis falls to 0 if avoided in patients with renal, liver or cardiopulmonary disease.
- Metformin differs considerably in both its structure and pharmacology from the traditional sulfonylurea oral hypoglycemics. Metformin has unique pharmacologic properties, a distinct mechanism of action, and adverse reaction and pharmacokinetic profiles that differ significantly from the sulfonylureas.

II. Pharmacology:

- Anti-hyperglycemic activity (Antidiabetic): The precise mechanism of metformin remains to be elucidated, its actions include decreased glucose production in the **liver**, enhanced insulin-stimulated glucose utilization in peripheral tissues (improved insulin sensitivity), particularly **skeletal muscle**, reduction of intestinal glucose absorption and, apparently, increased insulin-stimulated glycogen synthesis (or reduced glycogenolysis). At the cellular level metformin facilitates glucose transport across membranes, apparently by stimulating glucose transporter activity.
- Low risk of hypoglycemia as evidenced by the fact that this drug does not lower glucose levels in euglycemic patients and does not cause hyperinsulinemia.

III. Therapeutics

- Metformin has been used in millions of patients in over 90 countries worldwide since the 1960s, thus its efficacy and safety profile is well documented. Metformin monotherapy in NIDDM patients not adequately controlled by diet is reported to reduce fasting plasma glucose concentrations by 20% and glycosylated hemoglobin by ca. 2%.
- Metformin monotherapy has been shown to control hyperglycemia as effectively as the sulfonylureas chlorpropamide, tolbutamide and glyburide, and is equally effective in both lean and obese NIDDM patients. In NIDDM patients whose hyperglycemia was not adequately managed with a sulfonylurea (glyburide) and diet, addition of metformin improved glycemic control, reducing fasting plasma glucose levels by 20% or more. The glucose lowering effects of such a combination is synergistic because metformin and the sulfonylureas have different mechanism of action.
- Results from numerous clinical trials with metformin have revealed a number of other unique pharmacologic actions and potential clinical advantages versus the sulfonylureas. The more significant of these include: **1). a lack of weight gain (sulfonylureas promote weight gain), 2). no increase in plasma insulin or hyperinsulinemia (and resultant hypoglycemia), 3). persistent efficacy (2-5 years) when used alone or in combination therapy, 4). positive changes in plasma lipid profiles (decreased TGs, modest LDL reduction (8%) and HDL**

elevation), 5). reduction of blood pressure, and 6). avoidance or delay in the need for insulin injections.

- Metformin Indication: As monotherapy, as an adjunct to diet to lower blood glucose in patients with Type 2 diabetes mellitus whose hyperglycemia cannot be satisfactorily managed on diet alone. Metformin may be used concomitantly with a sulfonylurea when diet and metformin or a sulfonylurea alone do not result in adequate glycemic control. Metformin is formulated with glyburide in a combination tablet named Glucovance in the following strengths:
 - GLUCOVANCE 1.25 mg/250 mg tablet
 - GLUCOVANCE 2.5 mg/500 mg tablet
 - GLUCOVANCE 5 mg/500 mg tablet

IV. Adverse Reactions and Contraindications:

- Adverse reactions associated with metformin are typically mild, transient and of **GI origin**. During chronic metformin therapy, less than 5% of patients were discontinued due to Inability to tolerate its GI side effects. Serious adverse reactions have been reported only rarely by patients taking metformin.
- Acute, reversible (transient) GI tract effects occur in 5-20% of patients treated with metformin and include metallic taste, diarrhea, nausea, vomiting, anorexia and a variety of other GI symptoms (bloating). In fact, the favorable effect of metformin on body weight may be due, in part, to its unpleasant GI tract effects. These effects may be minimized by taking the drug with or after food and by initiating therapy with lower doses. Most GI reactions disappear when the dosage is lowered or the drug is discontinued.
- Biguanides such as metformin and phenformin are capable of producing concentration-dependent inhibition of lactate metabolism that can result in lactic acidosis, particularly in patient populations listed below (contraindications). Even a temporary reduction in renal function such as occurs after pyelography or angiography, can result in lactic acidosis in patients receiving biguanides therapy. To date the occurrence of this adverse reaction in patients treated with the recommended dosage of metformin appears to be rare in patients with normal renal function (0.03 cases/1000 patient years). When acidosis emerges, metformin should be discontinued. The drug should be also discontinued two days before procedures that reduce renal function and restarted only after renal function returns to normal. Excessive alcohol intake, which also causes lactic acidosis, and conditions associated with hypoxemia such as heart failure, shock,
- Hepatic failure and surgery also are indications to discontinue metformin. Also, about 10-20% NIDDM patients should be excluded from metformin therapy because of renal insufficiency. To minimize the incidence of drug-related lactic acidosis, patients should be monitored for renal (serum creatinine clearance) and hepatic sufficiency/disease as well as other medical conditions that increase tissue lactate production.

- It should be noted that metformin does not induce hypoglycemia, and the incidence of lactic acidosis with metformin is lower than the incidence of hypoglycemia induced by the sulfonylureas. Caution: metformin/glyburide combination formulations may cause hypoglycemia (due to glyburide).
- Contraindications: **Biguanides may increase the risk of lactic acidosis in patients with a history of alcoholism, liver disease, renal disease, pregnancy and lactation and CHF or patients with CV disease and chronic cardiopulmonary disease.** Metformin should be stopped for at least two days prior to radiographic dye studies since these dyes may be hyperosmolar and induce dehydration, increasing the incidence of acidosis.

V. Drug Interactions

- Metformin is not metabolized in human tissues, hence **metabolic-based** drug interactions are not known to occur.
- Cationic drugs that are eliminated by tubular secretion may compete with metformin for elimination and this may result in clinically significant interactions. For example, cimetidine (Tagamet) competes with metformin for elimination, resulting in increased serum concentrations (60%) AUC (40%) of metformin. Metformin, however, does not appear to alter the kinetics of cimetidine when these drugs are used concurrently. Thus patients taking metformin with other cationic drugs (procainamide, quinidine, trimethoprim, vancomycin) that may compete for elimination should be monitored carefully.
- Coadministration of metformin and furosemide is reported to result in increased C_{max} (22%) and AUC (15%) for metformin and decreased C_{max} (31%), AUC (12%) and terminal half-life (32%) for furosemide. These interactions do not appear to be related to altered renal clearance, and their significance remains to be established.
- Metformin also decreases the absorption of Vitamin B12 and folic acid, and therefore may produce a deficiency of these vitamins.
- In a number of studies no significant pharmacokinetic or pharmacodynamic interactions were noted when metformin was used concurrently with glyburide, nifedipine, propranolol or ibuprofen. However, caution should be exercised when metformin is administered concomitantly with drugs that may cause hyperglycemia.

VI. Pharmacokinetics:

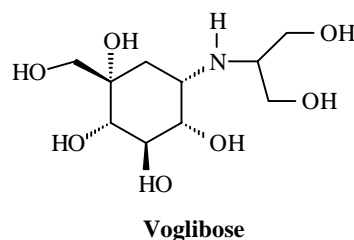
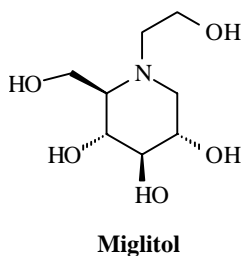
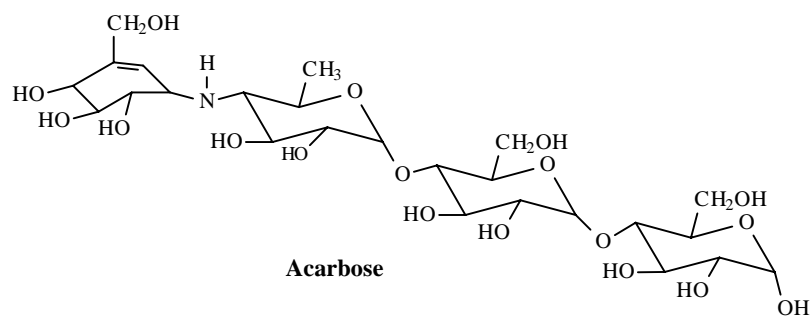
- Metformin has an absolute bioavailability of 50-60% (drug polarity limited absorption) and GI absorption is apparently complete within 6 hours of oral administration (**peaks in 1.5 to 2 hours**). Higher doses are proportionately less bioavailable over a dose range of 500-1500 mg. Also, food delays and reduces the extent of absorption.

- Metformin is rapidly distributed following absorption and displays minimal plasma protein binding. It rapidly accumulates in GI, renal and hepatic tissue and a small fraction slowly transfers to a deep compartment, presumably red blood cells.
- No metabolites or conjugates of metformin have been detected.
- The drug is excreted **renally by tubular secretion (and some filtration)**, and this elimination profile represents a site of potential drug interaction. Initial elimination from the plasma is rapid with a mean plasma half-life of 4.0-8.7 hours. A slower, terminal elimination phase occurs with a half-life approaching 18 hours. However, this phase represents only a small fraction (5%) of the absorbed dose and most likely accounts for the gradual elimination from the deeper compartment. Elimination half-life is prolonged in patients with renal impairment and this correlates with creatinine clearance.

Alpha-Glucosidase Inhibitors: Acarbose (Precose®) and Miglitol (Glyset®)

I. Development

- Slowly absorbable or lente carbohydrates and high fiber diets have been proposed as methods to delay glucose absorption and thus to blunt the postprandial increase in plasma glucose and insulin levels. While these dietary manipulations have been shown to be effective, most patients find the regimen difficult to follow.
- An alternative approach to prevent postprandial hyperglycemia involves the use of drugs that function as competitive inhibitors of small intestinal brush-border **alpha-glucosidases**. By inhibiting these enzymes the digestion of nonabsorbable, poly- and oligosaccharides (starch, sucrose) is prevented and thus the formation of absorbable monosaccharides (glucose, fructose) is delayed. The efficacy of this approach was supported by the introduction of acarbose (Precose®) several years ago. Acarbose, a pseudo-oligosaccharide isolated from the culture broths of various actinomycetes, reduces postprandial plasma glucose and insulin responses and improves metabolic control in NIDDM when combined with diet alone or with a sulfonylurea and a biguanide.
- Miglitol is the second alpha-glucosidase inhibitor approved for the treatment of Type II (NIDDM). In July of 1996 miglitol was authorized for marketing in the Netherlands under the trade name Diastabol®. In December of 1996 the FDA granted clearance for the marketing of miglitol in the US. Miglitol is a simple aminosugar derivative
- Voglibose, a simple amine substituted cyclohexane polyol is in development.



II. Pharmacology and Therapeutics

- Acarbose and miglitol differ significantly from the sulfonylureas and biguanides in their mechanism of action. They function as a high affinity, reversible inhibitor of intestinal alpha-glucosidase enzymes, particularly pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase. Pancreatic alpha-amylase hydrolyzes complex carbohydrates to oligosaccharides in the lumen of the small intestine while intestinal glucosidase hydrolyzes oligosaccharides, trisaccharides and disaccharides to glucose and other absorbable monosaccharides in the brush border of the small intestine (see Figure on next page).
- The inhibition of these enzymes thus reduces the rate of formation of "absorbable sugars" and thus delays the rise in blood glucose concentration following meals (postprandial). This action therefore results in attenuation of postprandial plasma glucose (30-35% reduction), as well as insulin, gastric inhibitory polypeptide and triglyceride peaks.
- The beneficial effects of acarbose on postprandial glucose levels have been confirmed in patients with NIDDM and IDDM. Data from clinical trials indicate that acarbose lowers postprandial and fasting blood glucose levels by about 20 and 10%, respectively and reduces glycosylated hemoglobin levels (0.6%) in NIDDM patients. The latter effect presumably occurs by an indirect mechanism. Postprandial insulin and triglyceride levels may occasionally be lowered. These actions also result in a rise in late postprandial plasma glucagon-like peptide 1 levels. Thus in individuals with normal or impaired glucose tolerance with hyperinsulinemia, α -glucosidase inhibitors decrease hyperinsulinemia and improve insulin sensitivity.
- Acarbose does not appear to exert any direct effect on insulin resistance in humans. Because of its different mechanism of action, acarbose enhances glycemic control when it is used in combination with the sulfonylureas. Also, acarbose decreases the insulinotropic and weight increasing effects of the sulfonylureas. Acarbose does not inhibit lactase and thus would not be expected to induce lactose intolerance.

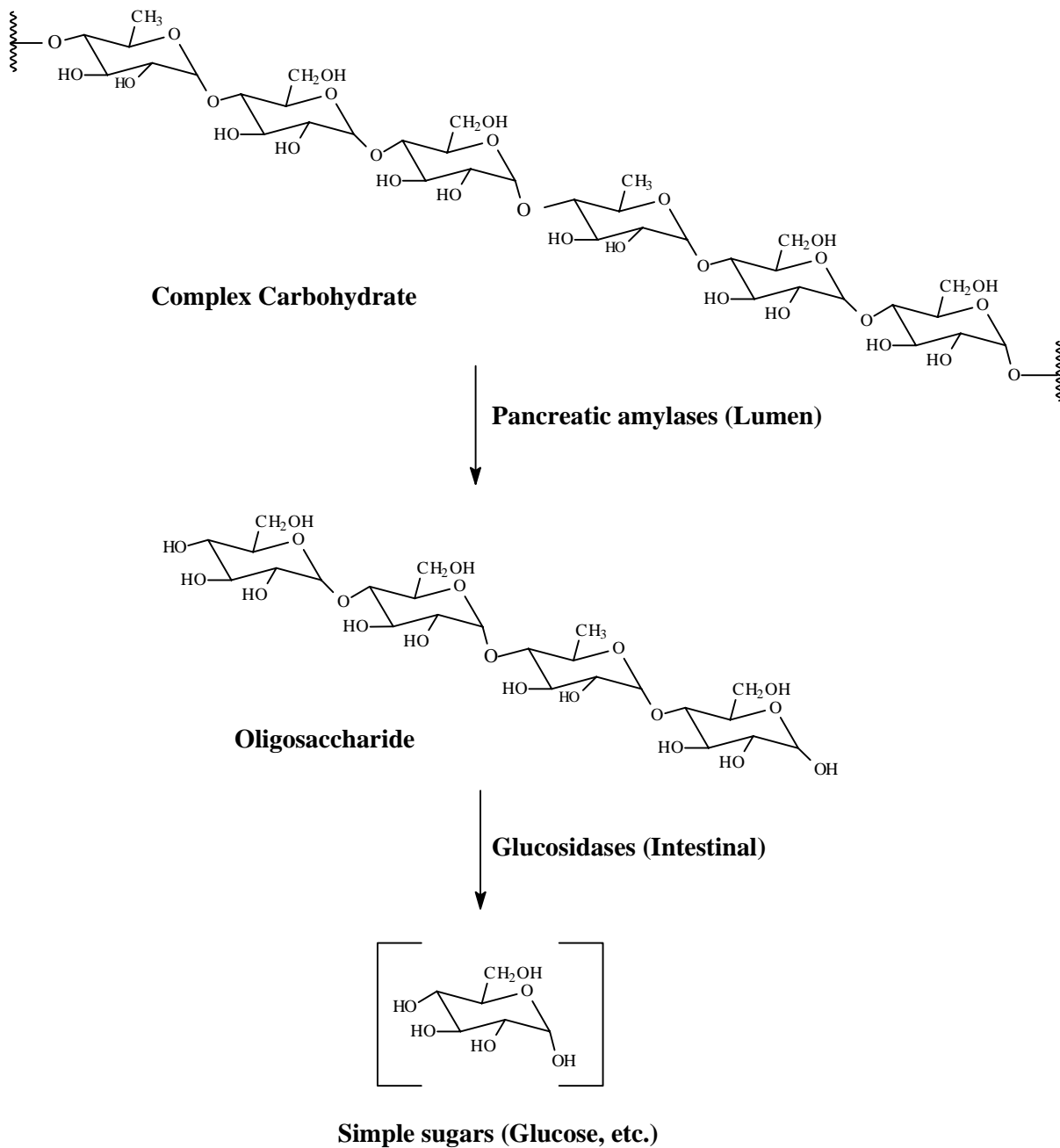
III. Adverse Reactions

- The most common adverse reactions associated with 50 to 300 mg tid acarbose therapy are gastrointestinal in nature and include flatulence (77%), abdominal pain and distension or bloating (21%), diarrhea (33%) and borborygmus. Abdominal pain and diarrhea typically improve upon continued therapy, and the intensity of flatulence also decreases. All of the GI reactions may be minimized by initiating therapy at low doses (25 mg t.i.d). The GI tract symptoms are a manifestation of the mechanism of action of these drugs and is related to the presence of undigested carbohydrate in the lower GI tract where they are fermented by bacteria. Thus these drugs should be avoided in patients with IBD and other GI tract disorders!
- Systemic adverse events associated with acarbose and miglitol have been reported only rarely. Anemia and elevated transaminase levels are reported to be significantly more common in acarbose than in placebo-treated patients, occurring in 3.8 and 1.1% of patients, respectively.

Small reductions in hematocrit may also occur, but these have not been associated with reductions in hemoglobin.

- Unlike sulfonylureas, miglitol and acarbose do not cause hypoglycemia, hyperinsulinemia or weight gain. Of course, hypoglycemia may occur when used with insulin or sulfonylureas.

Hydrolysis of complex carbohydrates and Oligosaccharides in Gut



IV. Drug Interactions

- Since acarbose and miglitol may potentiate the hypoglycemic effects of insulin and the sulfonylureas, the doses of these agents may require adjustment when used concurrently. When acarbose is used, hypoglycemia will not respond as efficiently to oral carbohydrates!
- The effects of acarbose and miglitol may be reduced by concomitant administration of intestinal absorbents such as charcoal and digestive enzyme preparations such as amylase and pancreatin. Digestive enzymes may breakdown miglitol particularly.
- The effects of acarbose and miglitol may be potentiated by concurrent administration of neomycin or cholestyramine. Acarbose interferes with metformin absorption
- Patients treated with acarbose and miglitol should be monitored carefully for loss of blood glucose control when drugs that produce hyperglycemia (thiazides, corticosteroids, estrogens, oral contraceptives, phenothiazines, thyroid products, phenytoin, nicotinic acid, isoniazid, sympathomimetics and calcium channel blockers) are administered concurrently.

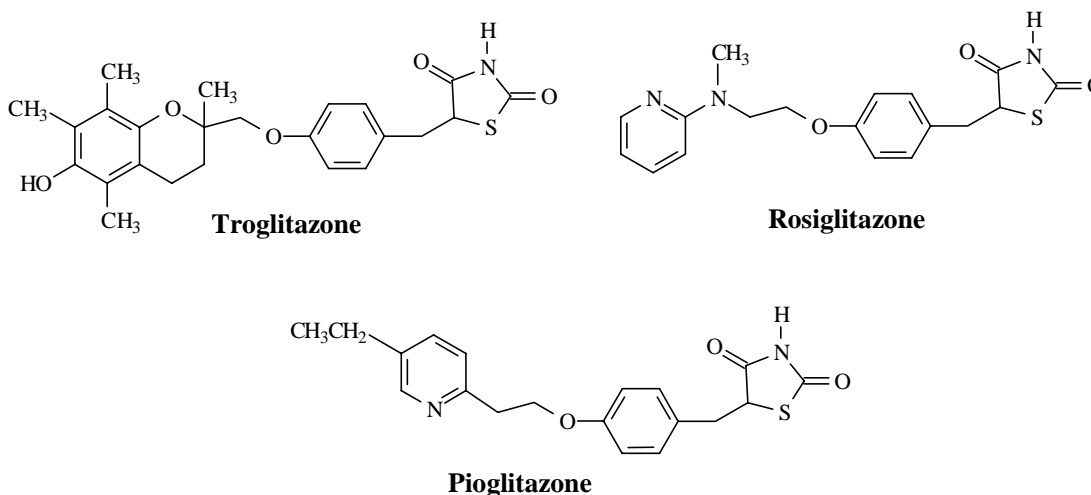
V. Pharmacokinetics

- Following oral administration to healthy volunteers, acarbose was found to be only minimally absorbed (<2%) in unchanged form. Because this drug acts locally within the GI tract, this low systemic bioavailability is therapeutically desired. **Administer with food!**
- The percent absorption of miglitol is dose dependent ranging from 100% at 25 mg to 50-70% at 100 mg. At therapeutic doses, peak miglitol levels are reached within 2-3h. **Administer with food!** Miglitol has a volume of distribution of 0.18 L/kg consistent with distribution primarily into the extracellular fluid. Plasma protein binding is negligible.
- Acarbose is rapidly and extensively metabolized by intestinal bacteria and digestive enzymes and the metabolites undergo biphasic absorption. The major metabolites have been identified as 4-methylpyrogallol conjugates. One of the minor metabolites formed by cleavage of a glucose moiety from acarbose retains therapeutic activity.
- Approximately 35% of the oral dose of acarbose is excreted in the urine, primarily as inactive metabolites. Nearly 50% of the oral dose is eliminated in the feces. The total body clearance of acarbose is about 600L/h and terminal elimination half-life of approximately 40 hours. Acarbose has a small volume of distribution (0.32 L/kg) and is minimally bound to plasma proteins at concentrations ≥ 1 ug/L. In animal studies acarbose metabolites were found to be secreted into breast milk and to penetrate placental barriers.
- Miglitol is not metabolized, and it is eliminated by renal excretion as unchanged drug. Thus drug accumulation is anticipated in renally impaired patients. Yet dosage adjustment to minimize accumulation is not feasible since miglitol acts within the GI tract. The elimination half-life of miglitol from plasma is approximately 2 hours.

Thiazolidinediones (Glitazones): Rosiglitazone (Avandia™) and Pioglitazone (Actos™)

I. Development and Pharmacology

- Troglitazone was the first thiazolidinedione marketed and was indicated for insulin-resistant patients who are receiving insulin and also as monotherapy. Troglitazone has since been removed from the market due to concerns of hepatic toxicity. However two new "glitazones" have been approved in recent years and these drugs specifically targets insulin resistance.



- The thiazolidinediones are dependent on the presence of insulin for activity, however, they do NOT affect insulin secretion. The thiazolidinediones are highly selective and potent agonists for the peroxisome proliferator activated receptor (PPAR) gamma that regulates the transcription of a number of insulin responsive genes. PPAR receptors can be found in key target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. For example, stimulation of these receptors may result in increased production of GLUT1 and GLUT 4 receptors. Additionally, PPAR-gamma responsive genes also play a role in the regulation of fatty acid metabolism. Unlike oral sulfonylureas, rosiglitazone enhances tissue sensitivity to insulin rather than stimulates insulin secretion. **Also, based on this mechanism, it may take several weeks for these drugs to fully express their activity (and thus to assess their potential).**
- Preclinical studies indicate that these drugs decrease hepatic glucose output and increase insulin-dependent glucose disposal in skeletal muscle. In animal models of diabetes, these drugs reduce the hyperglycemia, hyperinsulinemia and hypertriglyceridemia characteristic of insulin-resistant states such as NIDDM.

II. Therapeutics

- Indications: Rosiglitazone is approved as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus either as monotherapy or in combination with metformin. Pioglitazone is administered once daily and is approved as monotherapy or in combination with insulin, metformin, or a sulfonylurea.

- Pioglitazone **monotherapy** at a dose of 45 mg/day over a 26-week period in type 2 diabetes patients elicited a 2.6% reduction in HbA1c compared to placebo and statistically significant reductions in fasting plasma glucose (FPG). The efficacy of pioglitazone in lowering HbA1c levels is similar to that found for both troglitazone and rosiglitazone.
- **Combination therapy:** The addition of rosiglitazone or pioglitazone to metformin therapy results in significant reductions in hyperglycemia compared to either of the agents alone. Can also be combined with sulfonylureas.
- The glucose lowering effects of the glitazones are relatively slow in onset often requiring 2 weeks, and as much as 4 to 6 weeks. Some clinicians continue patients on the same doses of their current antihyperglycemic therapy when initiating glitazone treatment. Many type 2 diabetes patients who also require insulin therapy are able to reduce their insulin dose after receiving a glitazone and, in several cases, are able to discontinue insulin use altogether.

III. Adverse Reactions:

- Minimal hypoglycemia: Hypoglycemia was observed in relatively few glitazone-treated patients to date. Aggressive insulin dosing in combination with glitazone is associated with further reductions in HbA1c but with an increased risk of hypoglycemia.
- In contrast to troglitazone no evidence of drug-induced hepatotoxicity was noted in clinical studies of pioglitazone or rosiglitazone. However, the FDA recommends monitoring hepatic function at the start of glitazones therapy and every two months during the first year of treatment. Patients should also be advised to monitor for signs and symptoms suggestive of hepatic dysfunction such as nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, or jaundice.
- Edema, hypoglycemia, paresthesias, and elevations of creatinine phosphokinase (CPK) have occurred in some pioglitazone-treated patients. Reductions in hemoglobin and hematocrit have also been observed. Glitazone therapy is not recommended for Class III and IV CHF patients and close monitoring of the fluid status of Class I and II patients is necessary.
- Glitazone-treat patients may experience weight gains in the range of 1 to 4 kg may occur perhaps improved due to glucose control. The glitazones are reported to produce increases in low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and total cholesterol. LDL-C is increased the least with pioglitazone. The LDL/HDL ratio is preserved, although with rosiglitazone, there is a lag time of several months before HDL-C rises relative to LDL-C. Triglycerides decrease with troglitazone and pioglitazone, whereas the effect with rosiglitazone is variable.

IV. Drug Interactions

- Pioglitazone and rosiglitazone do not inhibit any of the major cytochrome P450 isoenzymes: troglitazone, the parent member of this series was a potent CYP3A4 isoenzyme inducer.

Studies are required to elucidate the potential interaction of inducers and inhibitors of the CYP3A4 isozyme with pioglitazone which is metabolized, in part, by this enzyme. The steady-state pharmacokinetics of glipizide and metformin are not altered by pioglitazone co-administration.

- Studies indicate that the incidence of hypoglycemia may be increased when glitazones are used with a sulfonylurea. Currently there are no controlled published studies on the hypoglycemic effects of troglitazone with the biguanides or alpha-glucosidase inhibitors.
- Oral contraceptives: Pioglitazone may induce the metabolism and reduce efficacy of OCs (some controversy over this interaction). Use additional protection or switch to rosiglitazone which does not alter OC clearance.

V. Pharmacokinetics

Key Pharmacokinetic Parameters

<i>Parameter</i>	<i>Rosiglitazone</i>	<i>Pioglitazone</i>
Bioavailability (Food effect)	99% (Minimal)	81-94% (Minimal)
T_{max} (Food effect)	1 hr (Minimal)	2 hrs (Delay)
PPB	99.8% (albumin)	>99% (albumin)
Vd, L/kg	0.2	0.63
Plasma t_{1/2}	100-160 hrs	3-7 hrs: Parent drug 16-24 hrs: Metabolites
Metabolism	Extensive! OND and AH (CYP2C8 primarily): Less active Glucuronide and Sulfate conjugates of oxidation metabolites: Inactive	Extensive! Oxidation by CYP2C8 and CYP3A4: <u>Active!</u>
Elimination half-live	3-4 hrs	16-24 hrs
Total renal Elimination	64%	15-30%
Total Fecal Elimination	23%	>60%?

- Absorption: Both glitazones are rapidly and extensively absorbed from the GI tract following oral administration. Peak plasma levels occur more rapidly with rosiglitazone and food may cause a greater delay in peak plasma levels (3-4 hours) with pioglitazone **but does not alter the extent of absorption**.
- Distribution: Both glitazones are extensively bound by plasma proteins (mainly albumin) and both have comparable volumes of distribution.
- Metabolism of Rosiglitazone: Rosiglitazone undergoes extensive metabolism with virtually no unchanged drug detected in urine. The major routes of metabolism include N-demethylation and

hydroxylation, followed by conjugation with sulfate and glucuronic acid. In vitro data show that rosiglitazone is predominantly metabolized by cytochrome P450 (CYP) isoenzyme 2C8, with CYP2C9 serving as a minor pathway. Metabolites are active, but have significantly less activity than the parent compound and are not expected to contribute to the insulin-sensitizing activity of rosiglitazone. Approximately 64% and 23% of an administered dose is eliminated in the urine and in the feces, respectively. The plasma half-life may range from 103 to 158 hours in normal patients. In patients with moderate to severe liver disease (Child-Pugh Class B or C), the oral clearance of unbound rosiglitazone is significantly reduced and the elimination half-life is prolonged roughly 2 hours compared to healthy patients.

- **Metabolism of Pioglitazone:** Pioglitazone is extensively metabolized by hydroxylation and oxidation. The major hepatic cytochrome P450 enzymes involved are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1 enzyme. Metabolites M-III and M-IV are the principal drug-related species found in human serum following multiple dosing and their concentrations are equal to or greater than serum concentrations of pioglitazone. Approximately 15—30% of the total pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted primarily as metabolites and their conjugates. Most of an oral dose is presumed to be excreted into the bile either unchanged or as metabolites and eliminated in the feces. The mean serum half-lives of pioglitazone and its metabolites is 3—7 hours and 16—24 hours, respectively.
- **Hepatic Monitoring:** The glitazones should be used cautiously in patients with **hepatic disease**. Although available clinical data show no evidence of glitazone induced hepatotoxicity or ALT elevations, these drugs are derivatives of troglitazone which has been associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death. It is recommended that patients treated with glitazones undergo periodic monitoring of liver enzymes and that glitazone therapy not be initiated in patients exhibiting clinical evidence of active liver disease or increased serum transaminase levels (ALT more than 2.5 times the upper limit of normal [ULN]). There are no clinically relevant differences in the pharmacokinetics of glitazones in patients with mild to severe **renal impairment** or in hemodialysis-dependent patients compared to patients with normal renal function.

Amylin (Pramlintide®) and Symlin ((Pramlintide acetate®)

Description: Pramlintide is an analog of human amylin, a hormone secreted by the pancreas to control blood glucose. Pramlintide is **under investigation** in several forms for the treatment of type II diabetes mellitus. Pramlintide is also known as tripro-amylin. Drug mimics the natural hormone (amylin) which is secreted from the beta cells of the pancreas and controls blood sugar and is deficient in diabetics; amylin is normally co-packaged with insulin in secretory granules and both are released in response to insulin secretagogues; a phase II study revealed that pramlintide significantly lowered fructosamine, a surrogate marker for glucose concentrations. The combination of amylin with insulin appears to improve glucose control over insulin alone and is compatible with insulin when mixed together in the same syringe.

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