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Evaluation of Tolbutamide in Treatment of Diabetes

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Abstract: *Tolbutamide is one of the most widely used antidiabetic agents. Its action is preferably connected with stimulatory action of β-cells in the pancreas, which results in intensive insulin secretion. It is used for type II diabetes mellitus of medium severity with no expressed microvascular complications.*

Keywords: Tolbutamide

I. INTRODUCTION

Tolbutamide is one of the most widely used antidiabetic agents. Its action is preferably connected with stimulatory action of β-cells in the pancreas, which results in intensive insulin secretion. It is used for type II diabetes mellitus of medium severity with no expressed microvascular complications.

Sulfonylureas are one of the oldest medications in the treatment of type 2 diabetes. These medications, first discovered in 1946 and released to the public 10 years later, work to stimulate the beta cells in the pancreas, thus promoting insulin secretion.

Tolbutamide is one of a class of compounds called sulfonylureas and was the first agent of this type to be widely administered. Though discovered in the 1940s, sulfonylureas were not used until the mid-1950s to control type II diabetes.17 Apr 2025 Sulfonylureas

Sulfonylureas are insulin secretagogues that bind to a pancreatic β-cell membrane receptor, promoting closure of hyperpolarizing adenosine triphosphate (ATP)-dependent potassium channels, cell membrane depolarization and exocytosis of insulin secretory vesicles. They are licensed for monotherapy or in combination with other OAAs except meglitinides. They are effective in reducing fasting plasma glucose, and in reducing HbA1c by about 10–20 mmol/mmol (1.5–2.0%) but are associated with weight gain and an increased risk of hypoglycaemia.

Gliclazide is commenced at a dosage of 40–80 mg given once or twice a day and increased to a maximum of 160 mg twice a day. Gliclazide MR is a modified- release preparation given once a day at the starting dose of 30 mg/day (equivalent to 80 mg/day standard-release gliclazide).

Glimepiride is taken once a day up to a maximum dosage of 4 mg/day; this can be increased to 6 mg/day in exceptional circumstances. In the UKPDS, 7% of patients taking a sulfonylurea experienced at least one severe hypoglycaemic episode over 9–12 months. These episodes can be prolonged and potentially dangerous with long-acting agents such as glibenclamide. Predisposing factors for the development of hypoglycaemia are age, liver, renal and cognitive impairment, and other interacting medications (listed in Appendix 1 of the British National Formulary (BNF)). Patients presenting with hypoglycaemia secondary to sulfonylurea use should be hospitalized and their blood glucose monitored for 24–48 hours; this is particularly important in older patients with renal impairment.

Agents such as glibenclamide and tolbutamide are very rarely used in practice and have been replaced by newer agents such as gliclazide that are relatively short-acting.

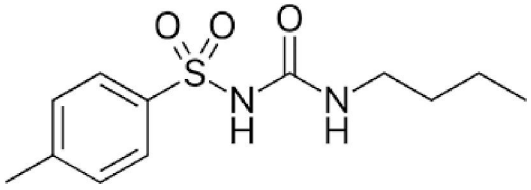

Fig 1 : Tolbutamide

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Tolbutamide, a first-generation sulfonylurea oral hypoglycemic agent, was discovered in 1956 and introduced commercially in Germany in 1957, becoming a cornerstone in treating type 2 diabetes. Here's a more detailed look at its history: Discovery and Development:

Tolbutamide was discovered in 1956 and is a first-generation sulfonylurea, a class of drugs that stimulate insulin secretion.

Commercialization:

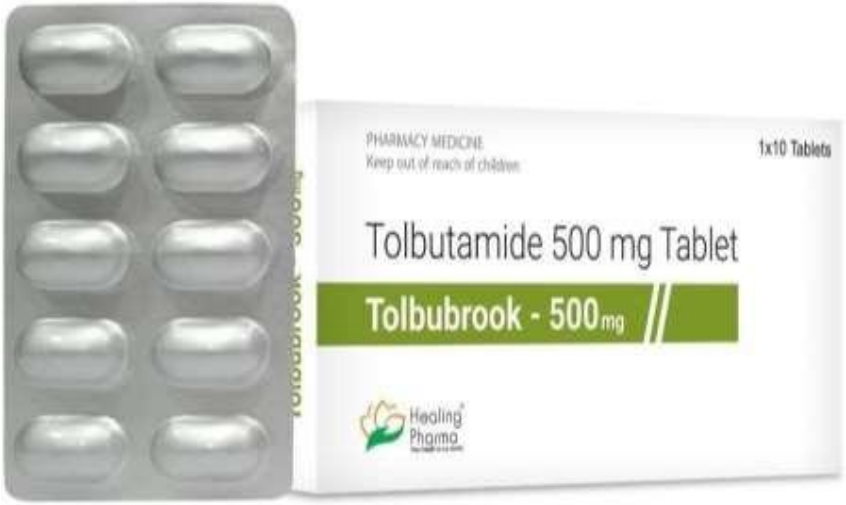
It was introduced commercially in Germany in 1956, followed by its FDA approval in 1957 to treat type 2 diabetes. Mechanism of Action: Tolbutamide stimulates the pancreas to release more insulin, helping to lower blood sugar levels. Brand Name:

It was sold under the brand name Orinase. First-Generation :

Tolbutamide was the first agent of this type to be widely administered, followed by other first-generation sulfonylureas like chlorpropamide, acetohexamide, and tolazamide. Second and Third Generations:

More potent second-generation sulfonylureas like glyburide and glipizide became available in the United States in 1984, followed by the third-generation sulfonylurea, glimepiride, in 1995. Current Use:

While sulfonylureas, including tolbutamide, are still used, they are often considered second-line treatment options after metformin for type 2 diabetes.



Tolbutamide

Advantages Of Tolbutamide:

- Tolbutamide is twice as potent as the related second-generation agent glipizide.
- Tolbutamide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body use insulin efficiently.
- The pancreas must be able to produce insulin for this drug to work.
-Tolbutamide is used to treat high blood sugar levels caused by a type of diabetes mellitus (sugar diabetes) called type 2 diabetes.

Disadvantages of tolbutamide :

- Tolbutamide is used to treat high blood sugar levels caused by a type of diabetes mellitus
- (sugar diabetes) called type 2 diabetes.
- indigestion o pain in the chest below the breastbone
- passing of gas
- Bleaching.

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- stomach pain, fullness, or discomfort
- Less common side effects
- flushing or redness of skin o unusually warm skin

Use of Tolbutamide :
- Tolbutamide is used to treat high blood sugar levels caused by a type of diabetes mellitus (sugar diabetes) called type 2 diabetes.
- In type 2 diabetes, your body does not work properly to store excess sugar and the sugar remains in your bloodstream.
- For type 2 diabetes:
- For oral dosage form (tablets):
- Adults—At first, 1000 to 2000 milligrams (mg) per day, taken in the morning or in divided doses. Your doctor may adjust your dose if needed. The dose is usually not more than 3000 mg per day.
- Children—Use and dose must be determined by your doctor.

Diabetes Mellitus is becoming fast growing epidemic all over the world. Despite several oral drugs available in the market, the most traditional as well as the most popular of them all are tolbutamide. tolbutamides have been a foundation for maintaining glucose levels in type II diabetes. Although having many side effects, this class of compounds is still being used as the second-line recommended choice of oral glucose-lowering treatment after metformin. In the present review, various stages involved in the development of these drugs have been discussed through important case studies. The mode of action of tolbutamide in biological system has been reviewed. Comparison of commercially available tolbutamide has been made while discussing their chemical synthesis and metabolism inside gastrointestinal tract.

This study was designed to focus on the genetic control of tolbutamide disposition in humans and to provide insight into the potential for high accrued blood levels in individuals receiving fixed dosage regimens. Tolbutamide was administered intravenously to 42 nondiabetic subjects, eight of their relatives, and to five sets of twins. A ninefold variation in the rate of tolbutamide disappearance from plasma (Kd) was found. This variation was characterized by a trimodal frequency distribution, suggestive of monogenic inheritance and consistent with pedigree analysis, indicating autosomal transmission of rapid and slow inactivation of tolbutamide. A heritability value of 0.995 for Kd indicated little influence of environmental factors on variation of this rate.

Interindividual differences in the binding of 35S-tolbutamide to serum proteins were also assessed. No correlation was found between tolbutamide serum protein binding affinity and Kd. Analysis of the metabolites of tolbutamide in urine samples provided evidence for the microsomal oxidation of the drug to hydroxytolbutamide as the primary site of genetic control.

In conclusion, this study provides evidence for monogenic control of tolbutamide metabolism in man. The results suggest that fixed dosage regimens of this drug, as were prescribed in the controversial University Group Diabetes Program study, might lead to higher accrued blood levels in slow inactivators.

Mechanisms of inhibition of tolbutamide metabolism: phenylbutazone, oxyphenbutazone, sulfaphenazole

Susan M Pond, Donald J Birkett, Denis N Wade

Clinical Pharmacology & Therapeutics 22 (5part1), 573-579, 1977 Tolbutamide half‐life was increased by chronic administration of sulfaphenazole (9.5 hr to 28.6 hr, n =2), phenylbutazone (7.9 hr to 23.1 hr, n = 8), and oxyphenbutazone (8.1 hr to 30.2 hr, n = 2). The rate of elimination of tolbutamide was decreased within I to 2 hr of a single dose of sulJaphenazole and the tolbutamide half‐life was increased from 9.2 hr to 25.7 hr (n = 2). In contrast, phenylbutazone and oxyphenbutazone, administered as single oral doses of 800 mg, had no immediate effect on tolbutamide elimination. At times greater than 20 to 30 hr after the single dose of phenylbutazone or oxyphenbutazone the rate of tolbutamide elimination was decreased. It is suggested that phenylbutazone and oxyphenbutazone act by inducing a form of cytochrome P‐450 with low activity for tolbutamide hydroxylation. whereas sulJaphenazole acts by direct inhibition of the microsomal mixed function oxidase system.

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Pharmacogenetics of tolbutamide metabolism in humans Joanne Scott, Phillip L Poffenbarger
Diabetes 28 (1), 41-51, 1978
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In conclusion, this study provides evidence for monogenic control of tolbutamide metabolism in man. The results suggest that fixed dosage regimens of this drug, as were prescribed in the controversial University Group Diabetes Program study, might lead to higher accrued blood levels in slow inactivators.
Method The trial was conducted on an out-patient basis. Patients were selected who were not grossly obese and had" mild" diabetes (as defined above) that could not be satisfactorily controlled by calorie and carbohydrate restriction alone. All our patients who were taking carbutamide and a few who were having insulin were transferred to tolbutamide. Those transferred from carbutamide were initially given the same dose of tolbutamide. Those who had been taking insulin were given reduced doses for a few days; the injections were then stopped and tolbutamide was started the next day. Patients who had had neither carbutamide nor insulin were observed on a strict low-carbohydrate diet for at leasta month, and if their mid-morning blood sugar remained above 200 mg. per 100 ml. they were given tolbutamide. The starting dose for these patients and forthose transferred from insulin was 0.5 g. two or three times daily, taken with the main meals. The dose was subsequentlyadjusted to a maximum of 4g. daily, according to the blood-sugar response.
Patients transferred from insulin were seen daily during the withdrawal period and for the first week of tolbutamide treatment. Special attention was paid to ketonuria, which was regarded as an indication for stopping the drug and resuming insulin treatment. Subsequently these and the other patients were seen weekly for the first month and then at least once monthly. At each visit a record was made of symptoms, weight, urine, and blood sugar, and the presence or absence of ketonuria and proteinuria. White blood cell and platelet counts were made monthly, and liver-function tests (serum proteins and electrophoresis, serum bilirubin and alkaline phosphatase, thymol turbidity, colloidal gold, and zinc sulphate flocculation tests) were performed when treatment began and subsequently every two or three months.
Mechanisms of inhibition of tolbutamide metabolism: phenylbutazone, oxyphenbutazone, sulfaphenazole.
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25.7 hr (n = 2). In contrast, phenylbutazone and oxyphenbutazone, administered as single oral doses of 800 mg, had no immediate effect on tolbutamide elimination. At times greater than 20 to 30 hr after the single dose of phenylbutazone or oxyphenbutazone the rate of tolbutamide elimination was decreased. It is suggested that phenylbutazone and oxyphenbutazone act by inducing a form of cytochrome P‐450 with low activity for tolbutamide hydroxylation. whereas sulJaphenazole acts by direct inhibition of the microsomal mixed function oxidase system.

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The role of the CFP2C9-Leu 359 allelic variant in the tolbutamide polymorphism Theresa H Sullivan-Klose, Burhan I Ghanayem, Douglas A Bell, Zhi-Yi Zhang, Laurence S Kaminsky, Gillian M Shenfleld, John O Miners, Donald J Birkett, Joyce A Goldstein Pharmacogenetics and Genomics 6 (4), 341-349, 1996 Tolbutamide undergoes hydroxylation in humans via a cytochrome P450-mediated pathway. The primary P450 isozyme responsible for this metabolism is thought to be CYP2C9. Population studies have indicated the existence of slow metabolizers of tolbutamide (~ 1 in 500) suggesting a rare polymorphism associated with 2C9. Several allelic variants of 2C9 have been identified; however, the effect of these allelic variations on metabolism in vivo is not established. In the present study, the coding regions, intron-exon junctions, and upstream region of CYP2C9 were amplified by PCR and sequenced in two slow metabolizers. One individual was homozygous for Leu 359/Leu 359 and the other individual was heterozygous for Arg/Cys 144 and for Ile 359/Leu 359. No other genetic variations in 2C9 were detected in these individuals. PCR- RFLP tests showed that Arg 144 Tyr 358 Ile 359 Gly 417 is the principle CYP2C9 allele. Frequencies of the rarer Leu 359 and Cys 144 alleles were
0.06 and 0.08, respectively, in a Caucasian-American population and 0.005 and 0.01 respectively in African-Americans. The frequency of the Leu 359 allele was 0.026 in Chinese-Taiwanese, but the Cys 144 allele was not detected in this population. Studies in a recombinant yeast expression system showed that the Leu 359 variant had the highest Km and the lowest Vmac for hydroxylation of tolbutamide of all the CYP2C9 allelic variants. This allelic variant also had the highest Km for the 7-hydroxylation of S-warfarin. The present data suggest that the incidence of the Leu 359 allelic variant of CFP2C9 may account for the occurrence of poor metabolizers of tolbutamide.
The excretion of tolbutamide in saliva of diabetic patients receiving single intravenous doses of 1 gm tolbutamide is described. Gas chromatography with electron capture was used for analysis. Pharmacokinetic parameters could be obtained from either salivary or plasma tolbutamide levels. There was a good linear relationship between tolbutamide concentration in saliva and in plasma; salivary levels were 1.2% of plasma levels. Equations are presented that account for the excretion in saliva based on extent of protein binding and degree of ionization of tolbutamide in plasma and saliva. Correlation of the saliva to plasma concentration ratio was extended to data in the literature on two other drugs.
The metabolic fate of tolbutamide in man and in the rat Tritium-labeled tolbutamide was found to be metabolized by man to l-butyl- 3-(p-hydroxvmethyl) phenyl-sulfonylurea as well as to the generally recognized metabolite, 1-butyl 3-(p-carboxy) phenylsulfonylurea. These two metabolites were the only drug-related materials detected in urine and together comprised 85% of an orally ad-ministered dose of tolbutamide. Both metabolites were isolated from urine in crystalline form and characterized. The carboxy metabolite accounted for 67% and the hydroxymethyl metabolite 33% of urinary radioactivity as determined by quantitative paper and thin layer chromatography. In the rat, 80% of an orally administered dose of tritium-labeled tolbutamide was excreted in urine, predominantly as l-butyl-3-(p-hydroxymethyl) phenyl-sulfonylurea, which was isolated in crystalline form and characterized. Small amounts of l- butyl-3-(p-carboxy)-phenylsulfonylurea and p-tolylsulfonylurea (together approximately 5% of drug-related material excreted in urine) were also detected by paper chromatography.
Orinase was developed by Upjohn Co. at a time when the primary medical treatment for diabetes was insulin injections. Eli Lilly had a lock on the market for insulin production at the time. The practical applicability of Orinase, like that of

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other treatments for disease states detected by paraclinical signs (such as lab test results) rather than clinically observable signs or patient-reported symptoms, benefited from increased sensitivity and availability of testing (in this instance, urinary glucose testing and later also fingerstick blood glucose testing). Milton Moskowitz (editor in 1961 of Drug and Cosmetic Industry) claimed that the introduction of Orinase, "expanded the total market by bringing under medical care diabetics who were formerly not treated."[3] It did this by changing the mindset about diabetes even more than insulin had. Treatment of this chronic disease was no longer seen as a mere slowing of "inexorable degeneration", but instead viewed through "a model of surveillance and early detection.

Orinase and other sulfonylureas emerged from European pharmaceutical research into antibiotics, specifically from attempts to develop sulfa compounds. One of the contenders for a new sulfa antibiotic had serious side effects during clinical trials at the University of Montpellier including blackouts, convulsions, and coma, side effects not observed with any other drugs in the sulfa cohort. An insulin researcher at the same university heard of these side effects and recognized them as common results of hypoglycemia. The resulting class of drugs for lowering blood sugar came to be known as the sulfonylureas, starting with Orinase and still in use today in other forms.

Unfortunately for diabetics dependent on insulin as a treatment for their condition, this research at Montpellier occurred in the early 1940s and was significantly disrupted by the German occupation of France during World War II. Development of these compounds was taken over by German pharmaceutical companies, which were obviously disinclined to share their bounty with nations upon which they were waging war. The German research was, in turn, disrupted by Germany's defeat in 1945 and the partition of Germany into East and West Germany. The sulfonylureas were trapped in East Germany. In 1952, someone smuggled a sample to a West German pharmaceutical company and research resumed. Clinical trials in diabetics began in 1954 in Berlin. In 1956, two different sulfonylureas were brought to market in Germany under the trade names Nadisan and Rastinon. American pharmaceutical companies in the postwar period had been seeking to establish business relations with the remnants of German pharmaceutical giants weakened by the war and partition of Germany. Upjohn (based in Kalamazoo until its purchase by Pharmacia in the 1990s) made deals with Hoechst, maker of Rastinon. The result was a cross-licensing agreement which produced Orinase.

Upjohn stood to open up a whole new arena of treatment for diabetes, one with a built-in and sustainable market, i.e. patient population. Just as two German companies brought sulfonylureas to market within the same year, Upjohn discovered Eli Lilly had begun clinical trials for carbutamide, another oral hypoglycemic. Upjohn pushed for large-scale clinical trials from 1955–1957, enrolling over 5,000 patients at multiple sites.

Upjohn's formulation was preferred when the Lilly formulation demonstrated evidence of toxicity in parallel trials at the Joslin Clinic. Lilly pulled carbutamide and halted development, leaving the field open for Upjohn to market its new treatment. In 1956, Upjohn filed for approval from the Food and Drug Administration. Jeremy A. Greene found the application's size – 10,580 pages in 23 volumes with 5,786 cases reports – was necessary to "render visible the relatively small improvements provided in less severe forms of diabetes." Indeed, Orinase was marketed by Upjohn not as a cure-all for all diabetics, but specifically as a treatment that was "not an oral insulin" and "did not work in all diabetics". Those were the instructions for marketing given to Upjohn's salespeople. As indicated by the FDA application, Orinase had been demonstrated "not to be effective in severe diabetes, but only in milder cases of the disease."[3]: 93 Orinase was one of a new class of drugs (including treatments for hypertension and hypercholesterolemia) aimed at providing marginal benefits over existing treatments for patients who had not previously been a target market for pharmaceuticals. As blood sugar testing for diagnosis of diabetes became more widespread, a curious side effect occurred: because blood sugar testing is not absolutely definitive in diagnoses of diabetes, more people were receiving borderline tests regarding their glycemic status. These borderline persons could be considered as being at risk for diabetes – prediabetic. Prediabetic patients have elevated blood sugar, but normal levels of sugar in their urine (glycosuria). Upjohn saw an opportunity to benefit and definitely market to a yet-greater expansion of the diabetic population, beyond even the "hidden diabetics" revealed by earlier public health campaigns. Upjohn also found a new use for Orinase: as a diagnostic. Orinase Diagnostic was added to the Orinase product line and, by 1962, was being sold as means of detecting prediabetes in that an abnormal response to Orinase following administration of cortisone in a "stress test" could be taken to indicate prediabetes. Orinase thus not only served to

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detect a previously hidden patient population, but also detected a patient population most likely to be interested in Orinase as a treatment for their newly diagnosed prediabetes. By the late 1960s, Orinase Diagnostic was withdrawn and the drug reverted to its therapeutic purpose. By that point, prediabetes had become a diagnosable and treatable condition which had dramatically increased the market for Orinase.

Orinase began to fall out of favor in May 1970 when asymptomatic prediabetics on long-term regimens of Orinase began to see news reports (beginning with the Washington Post) that Orinase may have serious side

effects including death from cardiovascular problems, according to a long- term study. In many cases, patients learned of this before their physicians, and also before FDA could advise relabeling the medication or suggesting alterations in appropriate usage. The question of whether Orinase did or did not increase cardiovascular problems has not been conclusively settled. The result was that Orinase and other medical treatments for prediabetes were "rolled back" by the FDA and practitioners in an attempt to focus on symptomatic patients for whom the risks of treatment might be balanced by the symptoms of the disease.

Pharmacia and Upjohn (now merged) stopped making Orinase in 2000, though a generic is still available and occasionally used.

Review of literature of tolbutamide:

Evolution of tolbutamide in the treatment of diabetes mellitus

1) Purabi Saha

Diabetes 2 (10), 2020

Diabetes Mellitus is becoming fast growing epidemic all over the world. Despite several oral drugs available in the market, the most traditional as well as the most popular of them all are tolbutamide. tolbutamides have been a foundation for maintaining glucose levels in type II diabetes. Although having many side effects, this class of compounds is still being used as the second-line recommended choice of oral glucose-lowering treatment after metformin. In the present review, various stages involved in the development of these drugs have been discussed through important case studies. The mode of action of tolbutamide in biological system has been reviewed. Comparison of commercially available tolbutamide has been made while discussing their chemical synthesis and metabolism inside gastrointestinal tract

Decisive factors in the tolbutamide controversy

2) Ralph B D'Agostino JAMA 232 (8), 825-829, 1975

No increased mortality trend attributable to tolbutamide is shown by an analysis of variance on logit-transformed data from the University Group Diabetes Program (UGDP) study. The UGDP's controversial finding of an increased rate with mortality subgrouped by "cardiovascular" causes is confirmed by the Biometric Committee's report, with reservations that failed to include overriding decisive factors. The basic problem is that inspected data set up the hypothesis (the increased cardiovascular mortality), and that the same data were used to test the …

3) JOHN S Boutagy,

British journal of clinical pharmacology 31 (6), 649-654, 1991

1. Six subjects participated in a detailed pharmacokinetic study of tolbutamide (pilot study). Using parameters based on these data, sixty‐ three non‐diabetic volunteers underwent a simple screening test designed to identify slow metabolisers of tolbutamide. 2. The screening test was an estimate of tolbutamide plasma elimination half‐life from plasma concentrations at 8 and 24 h after 500 mg tolbutamide orally, and urinary recovery of the hydroxy‐ and carboxytolbutamide metabolites over the 4‐8 h post‐dose period. 3. The mean tolbutamide half‐life for 61 of the screened subjects was 7.5 +/‐ 1.5 h (range 5.2‐ 12.2 h). Two subjects had half‐lives of 21.6 and 16.1 h. Their urinary metabolite recoveries were within the range of those in the screening test but lower than those in the pilot study. 4. The subject with the 21.6 h half‐life was restudied with intensive serial sampling for 72 h post‐ dose. She was confirmed as a ‘slow’ metaboliser of tolbutamide since her terminal half‐life was 25.9 h but plasma Cmax and tmax were within the range of those in the detailed study. This subject's 24 h urinary recoveries of both

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hydroxytolbutamide and carboxytolbutamide were clearly different from the mean values for the pilot study subjects implicating hydroxylation of tolbutamide as the metabolic defect.

5. The two point plasma half - life is therefore a discriminatory screening test but a 4 - 8 h urinary recovery is not. 6. A partial family study did not provide conclusive evidence of the inheritance of slow tolbutamide metabolism but the screening test should allow simple identification of slow metabolisers for further study.

Need Of Study:

This study was designed to focus on the genetic control of tolbutamide disposition in humans and to provide insight into the potential for high accrued blood levels in individuals receiving fixed dosage regimens. Tolbutamide was administered intravenously to 42 nondiabetic subjects, eight of their relatives, and to five sets of twins. A ninefold variation in the rate of tolbutamide disappearance from plasma (Kd) was found. This variation was characterized by a trimodal frequency distribution, suggestive of monogenic inheritance and consistent with pedigree analysis, indicating autosomal transmission of rapid and slow inactivation of tolbutamide. A heritability value of 0.995 for Kd indicated little influence of environmental factors on variation of this rate.

Interindividual differences in the binding of 35S-tolbutamide to serum proteins were also assessed. No correlation was found between tolbutamide serum protein binding affinity and Kd. Analysis of the metabolites of tolbutamide in urine samples provided evidence for the microsomal oxidation of the drug to hydroxytolbutamide as the primary site of genetic control.

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Effects of tolbutamide on vascular ATP-sensitive potassium channels in humans PJ Bijlstra, FGM Russel, Th Thien, JA Lutterman, P Smits Sulfonylurea (SU) derivatives exert their hypoglycemic effect by blockade of adenosine-5′ - triphosphate-sensitive potassium (K ATP) channels in the beta cell of the pancreas. Interestingly, K ATP channels also occur in the cardiovascular system, where they are thought to play an important role in cardioprotective mechanisms against ischemia. We have recently shown that the classical second generation SU-derivative glibenclamide is able to block vascular K ATP channels in man, whereas the newly developed second generation derivative glimepiride was devoid of this property. The aim of this study was to determine whether the first generation SU derivative tolbutamide has K ATP channel blocking properties in humans. In a group of 12 healthy male non-smoking volunteers, we investigated whether therapeutic concentrations of tolbutamide were able to inhibit the forearm vasodilation in response to the infusion of the K ATP channel opening drug diazoxide into the brachial artery. Changes in forearm blood flow were recorded by venous occlusion mercury-in-silastic strain-gauge plethysmography. above 200 mg. per 100 ml. they were given tolbutamide. The starting dose for these patients and forthose transferred from insulin was 0.5 g. two or three times daily, taken with the main meals. The dose was subsequentlyadjusted to a maximum of 4g. daily, according to the blood-sugar response.

Aim & Objective :

Preparation of tolbutamide for to control Sugar level and increase the level of insulin in body.

Objective:

Tolbutamide is used to treat high blood sugar levels caused by a type of diabetes mellitus (sugar diabetes) called type 2 diabetes. In type 2 diabetes, your body does not work properly to store excess sugar and the sugar remains in your bloodstream. Tolbutamide is used to treat high blood sugar levels caused by a type of diabetes mellitus (sugar diabetes) called type 2 diabetes. In type 2 diabetes, your body does not work properly to store excess sugar and the sugar remains in your bloodstream.

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Tolbutamide (oral route)The main objectives of diabetes mellitus management are to achieve and maintain near-normal blood glucose levels to prevent or delay complications, improve quality of life, and potentially prevent the onset of diabetes. This involves a multifaceted approach that includes medication, lifestyle modifications, and patient education.
1. Achieving and Maintaining Near-Normal Blood Glucose Levels: Goal: To keep blood sugar levels as close to normal as safely possible.
Target ranges: Before meals, the target range is typically 80-130 mg/dL (4.4-7.2 mmol/L), and after meals, it should be no higher than 180 mg/dL (10 mmol/L) two hours after eating.
Importance: Strict glycemic control minimizes the risk of both microvascular (eye and kidney disease) and macrovascular (heart and blood vessel disease) complications.

2. Preventing or Delaying Complications:
Microvascular complications: Diabetic retinopathy (eye damage), nephropathy (kidney damage), and neuropathy (nerve damage).
Macrovascular complications: Coronary artery disease, stroke, peripheral artery disease.
Preventive measures: Control of blood glucose, blood pressure, and cholesterol levels, along with smoking cessation.

3. Improving Quality of Life:
Patient education and empowerment:
Teaching patients about diabetes management, self-monitoring, and lifestyle modifications.
Addressing psychological and social aspects:
Supporting patients in adapting to a chronic condition and promoting healthy coping mechanisms.

4. Preventing the Onset of Diabetes:
Target populations:
Individuals at risk for developing type 2 diabetes, such as those with prediabetes or a family history of diabetes.
Interventions:
Lifestyle changes, including diet and exercise, and potentially medication.

5. Other Important Objectives:
Addressing co-existing conditions:
Managing hypertension, hyperlipidemia, and other conditions that can exacerbate diabetes-related complications.
Patient education and self-management:
Empowering patients to actively participate in their care and make informed decisions about their treatment plan.
Regular screening and monitoring:
Routine check-ups, including HbA1c testing, eye exams, and foot exams, to monitor disease progression and detect complications early

6) Tolbutamide is twice as potent as the related second-generation agent glipizide. Tolbutamide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the body use insulin efficiently. The pancreas must be able to produce insulin for this drug to work.

Plan of work:
Oral antidiabetic drugs are widely used in the treatment of diabetes mellitus and are effective in controlling blood glucose levels. These drugs are of several distinct types with different modes of action and include sulfonylureas, biguanides and α-glucosidase inhibitors. The sulfonylurea antidiabetic drugs include acetohexamide, acetylcarbutamide, carboxytolbutamide, carbutamide, chlorpropamide, glibenclamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepide, metahexamide, tolazamide and tolbutamide

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PHARMACOGENETICS OF TOLBUTAMIDE METABOLISM IN HUMANS.

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Material And Method :

Material :

Material	Property
P- toluenesulphony amide (sodium salt)	Versatile and used as plasticizer in the dyes and pharmaceuticals
Colloidal silicon dioxide	Used in industry it acts as anti caking agent thickening agent and flow improvers
Magnesium stearate	Using in industry, primary used as lubricated agent
Microcrystalline cellulose	It serves as emulsifier or bulking agent It binds the diluents and disintegrates in tablet formulation
Sodium Lauryl sulfate	Synthetic surfactant widely used in personal care and house hold cleaning product
Starch glycolate	It helps to tablet and capsules break down and dissolve more quickly when they come in the contact of water

Method :

• Tolbutamide is a first-generation potassium channel blocker, sulfonylurea oral hypoglycemic medication. This drug may be used in the management of type...ATC code V04 (section V04B Urine tests)

• issues of the ATC classification may include additional codes not present in this list, which follows the WHO version. Empty group V04CA01 Tolbutamide V04CA02

• Cholesterol (redirect from Biosynthesis of cholestorol) the chemical suffix -ol for an alcohol. Cholesterol is essential for all animal life. While most cells are capable of synthesizing it, the majority of cholesterol

• Metformin (redirect from Adverse effects of metformin) between octanol and water) of −1.43. These chemical parameters indicate low lipophilicity and, consequently, rapid passive diffusion of metform Disulfiram (nitroimidazoles), e.g., metronidazole First-generation sulfonylureas, e.g., tolbutamide and chlorpropamide Several cephalosporin drugs, including cefoperazone...

• Tirzepatide (category Chemical articles having Jmol set)

• tirzepatide showed minor improvement of reductions (2.01%–2.30% depending on dosage) in glycated hemoglobin tests relative to the injected GLP- 1 analog... Tetrodotoxin (category Chemical articles with multiple compound IDs)

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• clear; presence of TTX-producing bacteria within an animal's microbiome is determined by culture methods, the presence of the toxin by chemical analysis, and...CYP2C9 (category Wikipedia articles incorporating text from the United States National Library of Medicine)

• phenytoin, and other routinely prescribed drugs such as acenocoumarol, tolbutamide, losartan, glipizide, and some nonsteroidal anti-inflammatory drugs. Chlorpromazine (category Multiple chemicals in Infobox drug)

• Chlorpromazine is in the typical antipsychotic class, and, chemically, is one of the phenothiazines. Its mechanism of action is not entirely clear but is believed to. Ketamine (redirect from Recreational use of ketamine)

• hydroxylated derivatives of ketamine (80%) followed by dehydronorketamine (16%) are the most prevalent metabolites detected in urine. In chemical structure, ketamine... Semaglutide (category Chemical articles having Jmol set)

• 2-aminoisobutyric acid and arginine, respectively. The substitution of the alanine prevents chemical breakdown by dipeptidyl peptidase-4. The lysine at GLP position...

Procedure :

Powder Form

Solid form tolbutamide

1. Synthesis of Tolbutamide:

Starting Materials: p-toluenesulfonamide and butyl isocyanate. Reaction: The synthesis involves an addition reaction between the two starting materials.: Dissolve p-toluenesulfonamide and butyl isocyanate in a suitable solvent (e.g., tetrahydrofuran). Add a catalyst like triethylamine.

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Allow the reaction to proceed under reflux or at room temperature. Work up the reaction mixture by removing the solvent and purifying the product.

2. Formulation of Tolbutamide:
Dosage Forms: Tolbutamide can be formulated into various dosage forms, including tablets, capsules, and liposomes. Tablets: Excipients: Combine tolbutamide with excipients like lactose, starch, and magnesium stearate.
Formulation:
Use techniques like direct compression or wet granulation to prepare tablets. Liposomes:
Method:
Tolbutamide can be incorporated into liposomes using techniques like physical dispersion or ether injection. Ingredients: Use phospholipids (e.g., soya lecithin) and cholesterol in different ratios.
Other Formulations:
Transdermal Patches: Tolbutamide can be formulated into transdermal patches using solvent casting techniques. Nanoparticles: Tolbutamide can be loaded into polymeric nanoparticles to improve its bioavailability and achieve sustained release

Observation and result :
The tolbutamide test, also known as a tolbutamide tolerance test, is used to assess insulin production and glucose levels in response to a drug that stimulates insulin release. Observation involves monitoring blood glucose and insulin levels over time after tolbutamide injection. Results can indicate the presence of conditions like insulinoma or hypoglycemia, with specific criteria for interpreting the findings.
Observations During the Test:
Blood Glucose:
A normal response involves a temporary decrease in blood glucose levels after tolbutamide injection, followed by a return to baseline within a few hours.
Insulin Levels:
Healthy individuals experience a rise in insulin levels after tolbutamide, followed by a gradual return to baseline.
Other Measurements:
In some cases, other parameters like C-peptide levels may also be measured. Results and Interpretation:
Normal Response:
A normal response indicates a healthy pancreatic beta-cell function, with appropriate insulin release and glucose regulation.
Abnormal Response:
Hypoglycemia: In individuals with hypoglycemia, blood glucose may drop excessively low after tolbutamide, and the test may be used to confirm the diagnosis.
Insulinoma: Patients with insulinoma often exhibit exaggerated insulin release and persistent hypoglycemia, with blood glucose levels remaining low for an extended period.
The tolbutamide test is a diagnostic tool used to assess insulin production and identify conditions like insulinoma or fasting hypoglycemia by observing the body's response to tolbutamide-induced insulin release. Abnormal responses,.

II. SUMMARY AND CONCLUSION

In conclusion, drug discovery and development is a complex, lengthy, and expensive process that involves multiple stages from target identification to clinical trials, requiring a multidisciplinary approach and rigorous scientific evaluation to identify potential drug candidates, optimize their properties, and ultimately bring a safe and effective treatment to market, while facing significant challenges like high failure rates and strict regulatory oversight; despite its complexities, successful drug development can significantly improve patient health by addressing unmet medical needs. Drug discovery is considered a high-risk endeavor with a high potential reward if a successful drug is developed.The tolbutamide test is a diagnostic tool used to assess insulin production and identify conditions like insulinoma or fasting

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hypoglycemia by observing the body's response to tolbutamide-induced insulin release. Abnormal responses, particularly prolonged hypoglycemia or exaggerated insulin release, can indicate underlying pancreatic or insulin-related disorders.

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