THE NORTHERN HOSPITAL

GLIBENCLAMIDE

"Two Nudes in the Forest" (or "The Earth Itself") oil on metal, 1939, Frida Kahlo.

"You know Frida is lesbian don't you. She teases and flirts with Georgia O'Keefe at Stieglitz's Gallery ....Women are more civilized and sensitive than men because men are simpler sexually. A man's sexual organ is in just one place. In women on the other hand its all over their body, and therefore two women together have a much more extraordinary experience....". (Diego Rivera to Lucienne Bloch, 1938)

"You can tell Boit (Bert), that I am now behaving reasonably well in the sense that I do not drink so many copiosas, (copious ones, huge goblets).....tears of Cognac, Tequila, etc.....this I consider another advance toward the liberation of ....the oppressed classes. I drank because I wanted to drown my sorrows, but now the damned things have learned to swim..."

Frida Kahlo, letter to Ella Wolfe, 1938.

Despite Lupe Marin's "memory" that as a girl Frida "drank tequila like a mariachi" - it was probably at this time (late 1930s) that she began to carry a little flask of cognac in her purse or hidden in her petticoats. Sometimes she carried liquor in a perfume bottle, which she whisked out from inside her blouse as if she wanted to douse herself with cologne, downing a swig so quickly that most people did not notice what she was doing. It was generally held that "Frida could drink any man under the table", and various of Dr Eloesser's letters to her contain affectionate admonitions to cut down on alcohol. She had given up her "cocktailitos", she would reply, and she was drinking only a daily beer….

As Frida drank, her behaviour became more and more "indecent", and less and less bourgeois. She adopted the mannerisms of what she saw as the true people of Mexico, the "pelados" (penniless Indians or city bums). Peppering her speech with popularisms and four letter words - groserias - that she picked up in the market place. She was not unique in this" Mexican women from the art or literary world bent on being as colloquially Mexican as possible often used foul language. But Frida used it with a special exuberance and biting wit. And, as with many of her compatriots, wild conviviality and laughter frequently carried a flip side of loneliness and the fatalistic acknowledgment of poverty and death: expressions that burst frequently from her lips like hijo de la madre chingada, or cabron, have a kind of violence to them, a mixture of joy and despair, and a defiant affirmation of the cursor's pride in being Mexican.

Hayden Herrera, "Frida", 1989.

One evening in 1938, Diego Rivera casually let slip to Swiss born American artist Lucienne Bloch, that his wife, Frida Kahlo was bisexual. Though Lucienne was shocked, Frida simply sat back and laughed. Her relationship with her husband Diego, whom she loved very much but found impossible to live with, mainly on account of his many affairs, was complex, and on occasions volcanic. Frida always maintained that there were two great disasters in her life, the first was a bus accident in September of 1925, when she was just eighteen years old, from which she sustained horrific injuries and was extremely lucky to survive, the second was the day she met, and fell in love with, the great Mexican Artist, Diego Rivera. The first misfortune left her with a lifetime of pain, suffering and an inability to bear a child to delivery. The second, was to lead to anger, loneliness, and depression.

Four things helped Frida cope with life. The first three were her Art, an anaesthesia to the pain of life, drugs in the form alcohol and opioids, which made her forget life, and her love of her animals as companions in her loneliness. The fourth was her insatiable drive for sex in her frantic need for intimacy and love, and as antidote to her husband's

infidelities which she put up with, but never truly came to terms with. This need was fulfilled by many, both men and women. Her countless heterosexual conquests were well known. She had an appetite for the famous, apart from her husband, Diego Rivera, they included, the Mexican painter and engraver, Ignacio Aguirre, the Catalan artist, José Bartoli, the German Art dealer, Heinz Berggruen, the Japanese-American Artist and landscape architect, Isamu Noguchi, the mathematician Communist, Jean van Heijenoort, the American Art dealer, photographer, and New York Gallery owner, Julien Levy, and the Hungarian - American photographer and Olympic fencer, Nickolas Muray. But her most famous conquest of all, was Leon Trotsky.

Although an inveterate womanizer, Diego Rivera could not abide by his wife's clandestine affairs. He did however sanction, and even encouraged Frida's lesbian affairs. Though Frida was always discrete regarding her extramarital heterosexual affairs, so as not to arouse the wrath of Diego, whom she fully believed was capable of vengeful murder, she took full advantage of his relaxed attitude to her lesbian affairs. Frida nonetheless had to be doubly discrete about these, should they be leaked out to the general public. Consequently far, far less is known about her clandestine lesbian liaisons, compared to her heterosexual ones. Her first boyfriend, at the age of fifteen, at the Mexican Preparatory School, Alejnadro Gomez Arias, later recalled, "Frida was sexually precocious. To her sex was a form of enjoying life, a kind of vital impulse". Her lesbian desires, however, seemed to have been either suppressed in her adolescence, or otherwise had become an acquired taste. According to Alejnadro it was in 1925, when Frida was looking for work, an older female employee of the Ministry of Education's Library seduced her. Frida in 1938, described the affair with one of her school "teachers" as a traumatic event, although it is unclear whether she meant the event itself was traumatic of if the fact that her parents had discovered it. If her attraction was for famous men then, apart from Leon Trotsky, it was nothing compared to the fame of the women she later seduced. Amoung he rumored conquests were, the Costa Rican-born Mexican singer, Chavela Vargas, the Italian photographer, model, actress, and revolutionary political activist for the International Communist Comintern, Tina Modotti, the Mexican-American Hollywood film star, Dolores del Río, and the American Artist Georgia O'Keeffe. Most enigmatically of all however, was her rumored relationship with the African - Native American Folies Bergère dancer and French Resistance activist, Josephine Baker, while she was in Paris in 1939, on the eve of the Second World War.

As almost everything in Frida's intimate life appear in her Art work, so too does her lesbianism, although this is far more subtly alluded to. In one work, "Two Nudes in the Forest" oil on metal, 1939, we see one of Frida's hallmark motifs, that depict the duality aspects of her psychological and subconscious milieu. Two women intimately embrace in a dual- type environment, both hostile, to the left is a dense jungle, while to the right, a barren desert plain. At the obvious level are the two aspects of Frida's cultural heritage, a fair skinned woman, representing her Germanic descent lies in the lap of a dark skinned woman, representing her Native American heritage. This duality image also appears in one of her most famous Surrealist-style works, "What I saw in the Water", 1938, as two small figures lying on a sponge adrift in Frida's bath. But on deeper level the image also alludes to Frida's lesbianism. In the jungle of "Two Nudes in the Forest" a spider monkey, symbol of lust, spies on the women, its tail coils around a vine, just as the vine coils around itself, mirroring their embraces. To the right is an inhospitable

plain, symbol of bareness and loneliness. Frida is not only lonely she is also barren and so unable to have children. According to one of Frida's lovers, the Hollywood actress Dolores del Rio, to whom Frida gave the painting as a gift, "the indigenous nude is solacing the white nude. The dark one is stronger". From the dark woman's blood red shawl, blood drips into the wounded fissured earth, symbol of her people's suffering. The women sit precariously on the edge of a precipice, their backs to the forbidding jungle. They have nowhere to go, but they have each other. We see another of Frida's strongest motifs in this work, the dense network of roots. They spring from the barren earth, to create new life in the jungle. Though the jungle seems at first forbidding the roots are a symbol of new life, and so new hope. It is an image from Durer, one of Frida's greatest heroes of the Renaissance, itself a time of rebirth and new hope.

Frida Kahlo never let life's pain and setbacks get the better of her. She always lived by her "plan B". In the physical agony of her chronic pain, she took solace in cognac, tequila, strong Mexican beer and opioids. Despite her petite size she could drink any man under the table. In the psychological pain of her barrenness, faithless marriage and loneliness she took solace in her clandestine affairs; with men when available, and when not, with women. In the complex condition of type II diabetes our "first line" medication remains metformin. Yet frequently, there will be contraindications to this agent. In these situations we live by Frida's lifelong philosophy; we must always have a "plan B". In situations of metformin contraindication, like Frida, we never admit defeat - our "plan B" comes to us in the form of the sulphonylureas.

Frida Kahlo and Chavela Vargas c. 1945 (photograph by Nickolas Muray).

GLIBENCLAMIDE

Introduction

Glibenclamide (also known as **glyburide**), (trade name in Australia "**Daonil"**, amoung others) is a second generation **sulfonylurea**, antidiabetic agent.

Sulfonylureas are **insulin secretagogues.**

They are used as a *second line* alternative to metformin when this agent cannot be taken, or they may be used in combination with metformin if diet, exercise and metformin alone do not control blood glucose levels adequately.

Hypoglycaemia is the most serious potential adverse affect of the sulfonylureas as a class. Severe hypoglycaemia, which may be prolonged and potentially lethal, can be induced by all sulphonylureas.

See also separate document on Sulfonylurea overdose (in Toxicology folder).

History

The sulfonylureas were discovered during the Second World War, by the French chemist **Marcel Janbon** and his co-workers.

They were studying the sulfonamide antibiotics as a treatment for typhoid. One derivative, a sulfonylurea was found to cause bizarre behavior in the animals they were experimenting on. It was discovered that the animals had become profoundly hypoglycemic.

Janbon then convinced a medical colleague, Auguste Loubatieres, to try the new agent as a treatment for his diabetic patients, to some good effect. Loubatieres, and others, later established that the sulfonylureas stimulated the beta cells of the pancreas to release insulin.

The therapeutic sulfonylurea agent, glibenclamide was developed in 1966 by Boehringer Mannheim and Hoechst.

Chemistry

Glibenclamide is closely related to the **sulfonamide antibiotics.**

Classification

There are currently 6 classes (6 oral and one injectable within the Incretin-based therapies) of non-insulin hypoglycemic agents available in Australia:

The two principle classes are:

1. **The Biguanides**:

These agents act by reducing hepatic glucose production (i.e. gluconeogenesis) and increasing the peripheral utilization of glucose.

Examples include:

- Metformin

2. **The Sulphonylureas**:

These agents act by increasing pancreatic insulin secretion and also possibly by enhancing peripheral sensitivity to insulin:

Examples include:

First generation:

- Tolbutamide (no longer used)

Second generation, (more potent, lower doses):

- **Glibenclamide**
- Gliclazide
- Glipizide

Third generation:

- Glimepiride

Other newer agents with less clinical experience include:

3. **Incretin-based therapies**:

Dipeptidyl peptidase - 4 inhibitors (i.e. **DPP - 4 inhibitors** or "**Gliptins**"):

These agents increase the concentrations of incretin hormones (GLP-1 and GIP) that are produced in the gut following ingestion of food; GLP-1 stimulates insulin release, and reduces glucagon secretion.

Examples include:

- Alogliptin
- Linagliptin

- Saxagliptin
- Sitagliptin
- Vildagliptin

Glucagon-like peptide-1 (GLP-1) receptor agonists:

These agents are synthetic analogues of GLP-1; they increase insulin secretion and reduce glucagon secretion and also cause a small reduction in appetite.

Examples include:

- Exenatide
- Liraglutide
- Dulaglutide

4. **Glucosidase inhibitors**:

These agents reduce the breakdown of complex carbohydrate in the gut, thereby reducing absorption of carbohydrate and hence insulin requirements

Examples include:

- Acarbose.

5. **Thiazolidinediones (or "Glitazones")**:

These agents reduce peripheral insulin resistance and hence insulin requirements

Examples include:

- Pioglitazone
- Rosiglitazone

6. **Sodium-glucose co-transporter 2 (or SGLT-2) inhibitors (or "Gliflozins")**:

These agents reduce glucose reabsorption in the kidneys.

Examples include:

- Dapagliflozin
- Empagliflozin

- Ertugliflozin

Preparations

Glibenclamide as:

Tablets:

- 5 mg.

Fixed combination preparations:

- Metformin with glibenclamide formulations are available.

  These have not been proven to be more effective than co-administered metformin and glibenclamide. They may be used to improve compliance for patients stabilized on metformin combined with glibenclamide using the standard tablets.

  They do not however have the dosing flexibility of *co-administered* metformin and glibenclamide standard tablets.[5]

Mechanism of Action

The sulfonylureas act by:

1. Increasing pancreatic insulin secretion (i.e an insulin "secretagogue" action)

   - This effect is dependent upon **functioning beta cells**. It improves the sensitivity of beta cells to physiological glucose stimulus.

2. Possibly enhanced peripheral sensitivity to insulin.

Pharmacodynamics

Onset of action is around **1.5 hrs.**

Duration of action is around **24 hours.**

Pharmacokinetics

Absorption:

- Glibenclamide is administered orally.

  Glibenclamide is variably absorbed (75 - 95%) after oral administration

Distribution

- Protein binding is high at 99 %.
- Glibenclamide can cross the human placenta.
- Glibenclamide is not excreted into human breast milk

Metabolism and excretion:

- Glibenclamide is completely metabolized in the liver, principally to a 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites also contribute some mild hypoglycaemic action.

  Metabolism is mainly via the CYP2C9 and to a lesser extent theCYP3A4 enzyme systems. This should be taken into account when glibenclamide is co-administered with inducers or inhibitors of CYP2C9.

  The metabolites are excreted in the bile and urine, approximately 50% by each route.

  This dual excretory pathway is qualitatively different from that of most other sulphonylureas, whose metabolites are excreted primarily in the urine.

- Elimination half-life is around 5 - 10 hours, however there is more **prolonged biological effect** due to the formation of active metabolites.

Indications

The sulfonylureas as a class are indicated for Type II diabetes mellitus in the following situations:

1. As a *second line* alternative to metformin when this agent cannot be taken
2. In combination with metformin if diet, exercise and metformin alone do not control blood glucose levels adequately.

Combining a drug that increases insulin secretion (such as a sulfonylurea) with one that improves insulin action (such as metformin) is therapeutically worthwhile; however, the use of *two different sulfonylureas* together is not a logical therapeutic approach since they compete with each other for the same beta cell receptor, and so this approach is **not** recommended.

Substitution with, or addition of, another sulfonylurea does not usually improve glucose control; instead, consider combined treatment with other antidiabetic drugs or insulin, monotherapy with insulin or triple therapy with metformin and insulin.

Contra-indications/precautions

These include:

1. Known hypersensitivity or allergy to glibenclamide.

    - There is a possibility of cross sensitivity to sulphonamides and their derivatives.

2. Insulin dependent diabetes (type 1 or juvenile onset diabetes) or in those with diabetes complicated by ketosis (contraindicated).

3. Treatment of diabetic ketoacidosis (contraindicated)

4. Significant renal impairment:

    - Dosage reduction may be required in severe impairment because of increased risk of hypoglycaemia; (glipizide or gliclazide preferred).

5. Severe hepatic dysfunction:

    - There is an increased risk of hypoglycaemia

6. Elderly patients are particularly susceptible to the hypoglycaemic action of the sulfonylureas

7. Risk factors for **hypoglycaemia:**

    These may include:

    - Alcohol
    - Other hypoglycemic agents in general
    - Intense or prolonged exercise
    - Deficient caloric intake
    - Severe endocrine disorders such as adrenal or pituitary insufficiency.

8. Acute significant illness in general (e.g. MI, coma, infection, trauma) - monitor blood glucose and urine ketones; substitute insulin treatment if glycaemic control is inadequate.

Pregnancy

Glibenclamide is a category C drug with respect to pregnancy

Category C drugs are those drugs which, which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialized texts should be consulted for further details

Glibenclamide use during pregnancy has not been associated with an increased risk of congenital malformations.

Meta-analyses of glibenclamide use during pregnancy have suggested there is no overall increased perinatal risk when compared to other therapies.

However, complications such as macrosomia, gestational hypertension or preeclampsia, neonatal hyperbilirubinemia and neonatal hypoglycaemia have been reported. A recent systematic review and meta-analysis concluded that glibenclamide should not be used for the treatment of women with gestational diabetes if insulin or metformin is available.

Dietary modification and insulin therapies are preferred during pregnancy.

Follow-up and monitoring of both maternal and fetal wellbeing by a multidisciplinary team is recommended to ensure good glycaemic control and satisfactory fetal growth.

Breast feeding

From the limited information available, glibenclamide has not been detected in breast milk and hypoglycaemia has not been observed in breastfed infants of women taking glibenclamide.

Glibenclamide is considered safe in breastfeeding.

Women who choose to breastfed their healthy full term infant while taking glibenclamide should (nonetheless) observe the infant for signs of hypoglycaemia.

Adverse Effects

These include:

1. **Hypoglycemia:**

    - This is the most serious potential adverse affect of the sulfonylureas as a class.

      Severe hypoglycaemia, which may be prolonged and potentially lethal, can be induced by all sulphonylureas.

    - The risk of hypoglycaemia is highest with sulfonylureas with long half-lives and renally excreted active metabolites, such as glibenclamide.

- Elderly patients are particularly susceptible to the hypoglycaemic action of the sulfonylureas

2. Weight gain

3. GIT Upset

4. Allergic reactions

    - Including dermatological hypersensitivity reactions.

Uncommonly:

5. Blood dyscrasias

6. Elevated liver enzymes.

Dosing

Adult, (and child >12 years):

- 2.5 - 20 mg daily in 1 or 2 doses (up to **10 mg** as **single dose**).

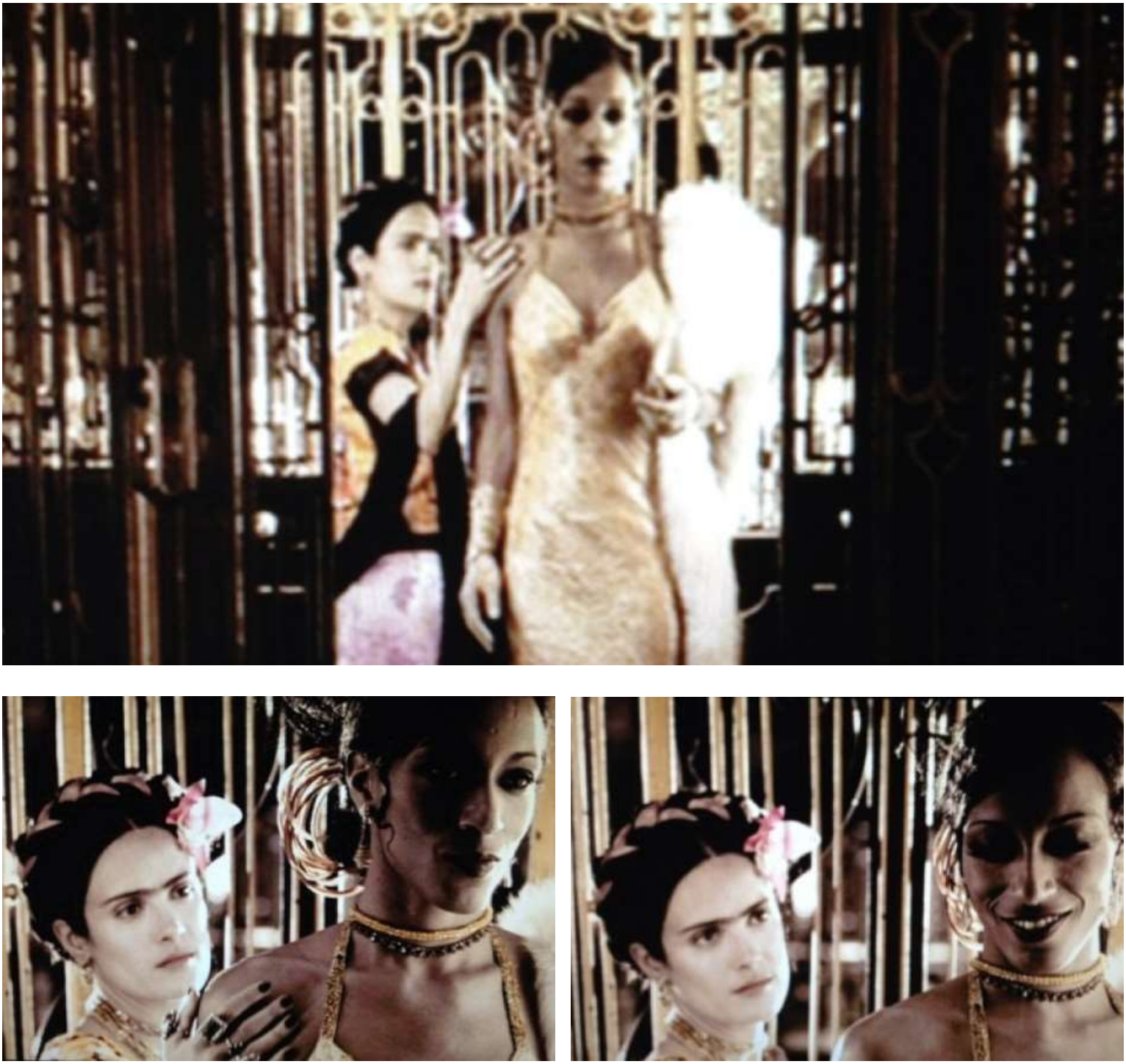
  Maximum daily dose **15 mg** if 12 - 18 years.

Start with low dose and increase slowly until glycaemic control is achieved.

Take with food to minimize the risk of hypoglycaemia.

It is very important *not* to skip meals after a sulfonylurea has been taken.

Dolores del Rio, c. 1938



Frida Kahlo (Selma Hayek) and Josephine Baker (Karine Plantadit-Bageot) in "Frida", 2002.

Above: Frida Kahlo and Josephine Baker, Paris, 1939

Left: Josephine Baker, c. 1926

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