THE NORTHERN HOSPITAL

INSULIN OVERDOSE

Gloria Swanson, Black and white silver gelatin photograph, 1924. Edward Steichen

At the end of the session I took a piece of black lace veil and hung it in front of her face. She recognized the idea at once. Her eyes dilated and her look had that of a Leopardess lurking behind leafy shrubbery watching her prey. You don't have to explain things to a dynamic and intelligent personality like Miss Swanson. Her mind works swiftly and intuitively..

Edward Steichen, 1924

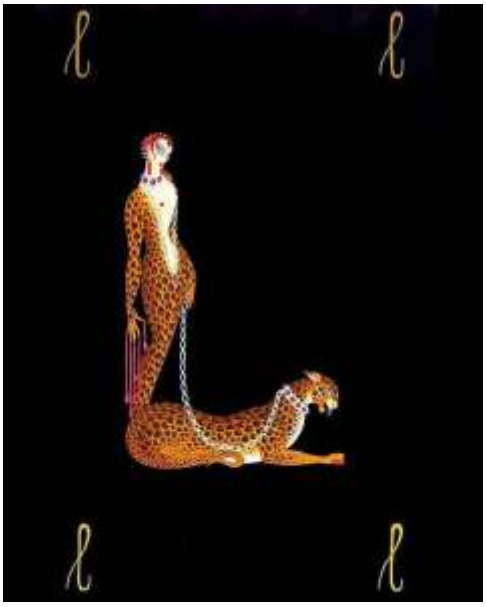
In the winter of 1923, Edward Steichen was at the top of his game. Famous on both sides of the Atlantic, he was renowned both as a painter and photographer, and just when things could not possibly have seemed better, he received the offer of a lifetime - the position of chief photographer for Conde Nast's high-end fashion and society magazines Vogue and Vanity Fair. Steichen jumped at the chance, and rest is history. For the next fifteen years he would utilize to the full the vast recourses of the Conde Nast empire to create a stunning oeuvre of that most glittering decade of the Twentieth century - the roaring 20s. As William A Ewing, Director of the Musee de l'Elysee, explains, he would put his unequalled brilliance to work "dramatizing and glamorizing contemporary culture and its high achievers in literature, journalism, dance, sports, politics, theater, film, and above all, the world of high fashion". Ewing is quick to point out that, although Steichen was not the first real fashion photographer, he was the very first and truly ***modern,*** *fashion photographer. He brilliantly combined his commercial work for agencies such as Chanel or Schiaparelli, with stunning portrait depictions of the stars - in an age when the term "star" actually meant something - and in so doing, gave unequaled publicity not only to the fashion house but also to, the star's latest Broadway production or Hollywood film. Ewing continues, "His influence on the field was immediate, and it proved to be long lasting….it is no exaggeration to say that he invented modern fashion photography…(he) elevated celebrity portraiture from the status of formulaic publicity stills to an aesthetically sophisticated genre in its own right…no other fashion photographer could rival Steichen for the range of haute couture he covered Alix (Gres), Callot Soeurs, Chanel, Lanvin, Lelong, Paquin, Poiret, Schiaparelli, Vionnet, Worth, and a host of other designers and fashion houses saw their works depicted creatively and convincingly on the pages of Vogue".*

As Steichen's fame grew he gained commissions to do photographic portraits of the rich, the powerful the famous from all walks of life - artists, actors, athletes, actors, musicians, politicians, writers, great statesmen, that included the likes of Cecil B DeMille, Winston Churchill, Franklin Delano Roosevelt H.G Wells, Colette, Greta Garbo, and Gary Copper. Steichen's works have created for posterity a stunning visual record the 1920s and early 30s, unrivaled in its brilliance. His genius in part lay in his ability to continuously reinvent. Says Ewing, "Though the incessant demands of the magazines meant that the lion's share of the shootings had to be accomplished in the studio, Steichen seems to have been oblivious to its physical constraints; he continually found new ways to frame his subjects, pose them and light them. If we look at most of the work of his studio-bound contemporaries…we find a more limited repertoire (a few standard props endlessly recycled and lit in each photographer's trademark fashion). Steichen by comparison, seems the younger, the more inventive, the more creative. At one moment, he is all baroque splendor; at the next he pares it down to streamlined simplicity. And as Carol Squiers notes in her informative essay, when the studio simply wasn't big enough to give reign to his imagination, Steichen took his models out into glamorous

environments. A photographer of lesser ambition would have settled into a comfortable routine, but Steichen needed to give it his all, every time".

As brilliant as Steichen's work was, we should note that he was also ***working with,*** *some of the most brilliant and talented people of the day. This kind of combination, can and often does result in iconic images that can define and document in permanent record for future centuries the oeuvre of a time. When one asks the question, "What was Steichen's greatest work", endless debate ensues and ultimately of course it becomes purely a matter of individual taste. But of all his stunning images one of them perhaps would universally be acclaimed as at least* ***one of*** *his greatest - the Leopardess - Gloria Swanson. At the end of a long photographic session with the Hollywood star of the silent silver screens of the 20s, Steichen playfully held up a black lace veil towards her. Gloria instantly seized it and reflexly put it near her face glaring back into Steichen's eyes, like a leopardess peering through the jungle at its intended prey. Steichen was thunderstruck by the image before him and seizing the moment, photographed her - recording an instant of reality - that would become an iconic image of age.*

Like Edward Steichen in his studio of the 1920s, we face many dramatic and unexpected interactions and situations in our everyone work in the ED - we must remain ever alert - even at the very end of a long tiring session. We hope to be able to deal with these unexpected, situations and like Ms Swanson be able to creatively adapt in an instant. When confronted with patients who overdose on insulin, the pharmacokinetic situation is quite different from the expected. The severity and the duration of symptoms in insulin overdose are unpredictable and will not be reliably dependent on the preparation administered. Like Ms. Swanson and Edward Steichen we need to be open minded, ready to adapt our thinking in an instant, and to expect the unexpected! Unlike Edward Steichen, sadly, we do not routinely find ourselves interacting with clients of the calibre of Ms. Swanson and so although an iconic image of our times is unlikely to be the result of our exciting interactions, at least by our adaptive thinking we may ensure a good outcome for our patient!.



Left: Gloria Swanson, Black and white silver gelatin photograph, c. 1924. Right: Leopard Woman, Romain de Tiroff Erte.

INSULIN OVERDOSE

Introduction

Deliberate insulin overdoses result in profound and prolonged hypoglycaemia which can be fatal or may result in permanent neurological damage.

Deliberate insulin overdose should be suspected in diabetic patients with unexplained severe and recurrent hypoglycaemia or in non diabetic patients who present with profound hypoglycaemia.

The severity and the duration of symptoms in insulin overdose are unpredictable and will not be reliably dependent on the preparation administered.

Prognosis is excellent providing patients are treated early with adequate glucose replacement.

Late presentation with established insulin induced coma correlates with a poor prognosis.

Physiology

Insulin is normally released from the beta pancreatic islet cells of the pancreas.

Insulin stimulates the transfer into the cells of:

- **Glucose**
- Potassium
- Phosphate
- Magnesium

Insulin also promotes the synthesis and storage of

- Glycogen
- Protein
- Triglycerides

Preparations

Modern insulin products are either human insulins or **insulin analogues** obtained by **recombinant DNA technology.**

The use of older preparations of **porcine** or **bovine** insulins is now rare.

There are a large number of preparations of human insulin analogs.

Some examples (generic and brands) include:

Rapid (or ultra short) (bolus) acting:

Lispro:

- Humulog

Glulisine:

- Apidra

Aspart:

- NovoRapid

Short acting (sometimes also referred to as soluble or regular) (bolus):

Neutral (human):

- Actrapid
- Humulin R
- Humulin

Intermediate acting (basal):

Isophane (protamine suspension):

Isophane human insulin is of recombinant DNA origin. It is a crystalline suspension of human insulin with protamine and zinc.

- Humulin NPH
- Protaphane
- Hypurin isophane

Long acting (basal):

Detemir:

- Levemir

Glargine:

- Lantus

Combination (biphasic premixed) preparations:

There are a very large array of these, some examples include:

Neutral / isophane:

- Humulin 30/70
- Mixtard 30/70

Lispro/ lispro protamine:

- Humalog Mix 25
- Humalog Mix 50

Aspart / aspart protamine:

- NovoMix 30

Pharmacokinetics

In overdose the pharmacokinetics of insulin are changed.

The duration of action can be greatly prolonged to days and this is independent of the type of preparation that is used.

Absorption from the injection site is both slowed and erratic.

Clearance of absorbed insulin is also prolonged.

Endogenous insulin is 60% degraded by the liver and 40% excreted by the kidneys.

Risk Assessment

Any insulin overdose is serious

Hypoglycaemia may last for days and the patient will require close monitoring throughout this period.

The severity and the duration of symptoms in insulin overdose are unpredictable and will not be reliably dependent on the preparation administered.

There are no *dose specific* effects.

Delayed presentation with established hypoglycaemic coma is associated with poor outcomes

Patients with renal failure will be at further risk because of decreased insulin clearance.

Clinical Features

The clinical features are those of hypoglycaemia.

Onset will usually be within 2 hours, but this may be delayed.

1. CNS symptoms:
    - Agitation/ restlessness
    - Confusion
    - Visual disturbances
    - Focal neurological signs such as hemiplegia are uncommon but possible.
    - Clouded conscious sate/ coma
    - Seizures
2. Autonomic features:
    - Diaphoresis
    - Tachycardia
    - Nausea/ vomiting

A hyperinsulinaemic state may persist for > 3 days.

Persistent untreated hypoglycaemia can result in permanent neurological deficit and death.

Investigations

1. FBE
2. U&Es/ **glucose**
    - Initially every 15 minutes during initial resuscitation and then at least hourly during subsequent dextrose infusions.
    - Also regularly check for **hypokalemia.**
3. Check and monitor phosphate and magnesium levels.
4. Alcohol / paracetamol level as indicated
5. ECG:

- For drug co-ingestion
- For hypokalemia and arrhythmias

6. Insulin/ C-peptide levels:

   - Insulin levels will be elevated but they do not correlate with the requirement of, or magnitude of, or duration of glucose treatment, and so are not clinically useful.
   - Insulin and C-peptides levels are helpful, in the very rare event that an endogenous hyperinsulinemic state needs to be excluded.

Management

1. Immediate attention to any ABC issues

   - IV access.

2. Glucose initial bolus if symptomatic or BSL is < 4.0 mmol/L:

   Adult:

   - Give 50 mls of 50 % glucose IV and repeat as necessary.

   Child:

   - Give 2- 5 mls/kg of 10 % glucose IV

   These bolus doses can be repeated as required

3. Glucagon:

   - This can be used as a temporizing measure to treat hypoglycaemia when IV access is difficult to achieve.
   - It is *not* however an adequate treatment on its own for insulin overdose.

4. Glucose infusion:

   - **10 % dextrose** infusion at 100 mls per hour (i.e 10 grams per hour).

     Asymptomatic hypoglycaemia (< 4 .0 mmol/L) is managed by increasing the rate of infusion without bolus therapy.

   - If this infusion is inadequate then a 25 % or 50 % dextrose solution may need to be infused via a **central line.**

     Infusion rates of around 150 mls /hr of 50% dextrose may be required for many days, (3-7)

Only withdraw glucose infusions gradually (and not at night, when observation may be more problematic).

Monitor patients for a further 4-6 hours post cessation of glucose infusion.

5. Potassium:

- Serum potassium levels must be carefully monitored and any hypokalemia corrected as necessary.

- 20 mmol/hr is a reasonable initial replacement rate

Disposition:

The severity and the duration of symptoms in insulin **overdose** are unpredictable and will not be reliably dependent on the preparation administered. [1]

For this reason a *prolonged* period of observation is usually recommended, especially for the longer acting insulins.

In *general terms*, patients should be admitted and closely observed for a minimum of **12-24 hours,** (*personal communication Dr Shaun Greene, April 2014*).

All insulin overdose patients with **hypoglycaemia** should be admitted to HDU/ICU for several days minimum.

Gloria Swanson, c. 1924, ...her look was that of a Leopardess!

References

1. Insulin overdose in L Murray et al. Toxicology Handbook 3rd ed 2015.

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