

LEVETIRACETAM (KEPPRA)



Lee Miller in Adolf Hitler's Bath, (black and white photograph, David Scherman) Munich 1945. The boots are those she was wearing at Dachau earlier that morning. The dirt on the bath mat is that of Dachau.

The young soldiers crammed shoulder to shoulder aboard the lurching transport were in a state of high alert, and high agitation. Nerves were on edge, the adrenaline surging through their veins, every sense heightened to fever pitch. They could see Omaha beach just ahead of them, and soon they would be landing. The beach had now been "secured"; or so they were told, artillery fire could be heard in the distance. The Americans had suffered heavy casualties, losing thousands, on the first days of the landing. Every man's heart was in his throat. Spitfires roared overhead. As the waves heaved the transport to one side, bayonets, guns and equipment flew in every direction. Tempers became frayed; "Hey watch those grenades buddy!" The adrenaline levels aboard the transports of course were always high as they approached the Omaha beaches, but this particular transport was at another level again, a woman was on board! Not only that, she seemed a real "high-class" dame. It was whispered among the troops that she had once been a Vogue model! No &^%\$! Lee Miller was on special assignment; photographer and war correspondent for Vogue magazine! Almost twenty years older than most of the soldiers, they felt they had their mother on board. Their commanding officers had warned them to keep their cussing and swearing to a minimum. "Hey get that goddam bayonet out of my face you SON OF A BITCH!". A ferocious glance from the sergeant... "sorry, sorry sorry ma'am, sorry..." But Lee could swear as well as any trooper in the entire US Third Army. She soon put the boys at ease with some well chosen phrases which shocked the entire transport, including the sergeant! The hatch slammed down onto the water with a tremendous splash - a frantic rush ensued - not to the beach but to Lee. "I'll carry you ashore ma'am" "No I will". "Get onto the goddam beach NOW you &^%ing sons o' bitches! Ill carry Miss Miller ashore", screams the sergeant. "Why thank you sergeant, I can see you are not only an officer, but a gentleman as well!". "Er yes why...thankyou ma'am". Lee could still flutter her eyes, when the situation required.*

Lee was in her element, as soon as she hit the beach (or rather was carried to the beach) she screamed "where's the goddam front; I've got pictures to take". Her commanding officers were nervous, there was no way they were going to let a woman anywhere near the front line fighting. They would send her to St Malo, it was said it had been secured. But it hadn't! Lee arrived to find fierce street fighting in progress. She would be the only allied female photographer to see front line active service in Europe. She took to the job immediately; in a state not of terror, but almost of exhilaration! Many of her photographs however would be confiscated or censored to her immense frustration, on the grounds of national security or of adversely affecting moral back home. She recorded; "A company files past, ready to go into action, grenades hanging on their lapels like Cartier clips". American bombers droned high overhead, Lee continued, "We heard them swelling the air like I've heard them vibrating over England. This time they were bringing their bombs to the crouching stonework 700 yards away. They were on time - bombs away - a sickly death rattle as they straightened themselves out and plunged into the citadel - deadly hit - for a moment I could see where and how - then it was swallowed up in smoke". Lee photographed these immense explosions. Without knowing it, she had recorded warfare's first use of napalm.

Later that day, Lee would experience the immediate terror of war first hand. Caught in sustained crossfire she frantically dove into one of the townships underground vaults. "I sheltered in a Kraut dugout, squatting under the ramparts. My heel ground into a dead detached hand....I picked up the hand and hurled it across the street and ran back the way I'd come, bruising my feet and crashing in the unsteady piles of stone, and slipping in blood. Christ....it was awful". The Germans eventually were overwhelmed by American airpower,

their own Luftwaffe absent from Normandy, the entire force fighting the Russians in the titanic struggle on the Eastern Front. The German leader Von Aulock, surrendered and the fighting in St Malo was over. The first to appear, arms upraised was Von Aulock himself. Lee immediately ran towards him flicking off continuous photographs. He hid his face and cursed at being photographed by a woman soldier - he could not stand the indignity. But Lee simply kept running in front of him, taking pictures over and over at close range. The GIs were amazed seeing Lee in action among the German prisoners freely "liberating" field glasses and various other items from them as took her fancy! The local French townspeople were astonished and repeatedly pointed to the "in your face" "femme soldat". Lee was with the US Third Army when it entered Paris. There she recorded the wild and unrestrained scenes of celebration and joy among Parisians on their liberation. Though she had no qualms about photographing female "collaborators" who had had their hair cut off and stripped naked, she did begin to feel some sympathy toward them in their humiliated and terrified state. Some of them out of desperation gravitated toward her as a woman for protection. No friend of the Nazis, she found her emotions confused. She stayed for a while in Paris following the liberation, even producing some fashion pieces for Vogue in an effort to lift moral back at home by recreating a sense of normality and to take people's minds off the horror of the conflict consuming Europe. In an emotional reunion, she tracked down Pablo Picasso, who had maintained a precarious existence in Paris throughout the occupation. The Nazis were no friend of Picasso as a producer of "degenerate art", some of their own nationals had been sent to concentrations camps for this 'crime'. But as a Spanish national, although continually harassed, he had been spared from the fate of the concentration camp. Lee and Pablo "liberated" much French champagne together as they caught up over nearly six years of lost time.

But soon Lee became restless again. She wanted to be where the front line action was. She rejoined the Third Army when it was finally ready to invade the German Reich itself. It would be a decision that would change her life. She would never be the same Lee Miller after experiencing firsthand what the Nazis truly represented. As the Third Army pushed deeper into Germany reports began to trickle back of unimaginable horrors. The first of the concentration camps that the Third Army came across was a place called Ohrdruf in the Thuringian Forest. On April 12, 1945, scarcely able to believe the reports, Generals Eisenhower, Patton and Bradley decided to see for themselves. Eisenhower later observed, "I have never felt able to describe my emotional reactions when I first came face to face with indisputable evidence of Nazi brutality....I have never at any other time experienced an equal sense of shock...I sent communications to both Washington and London, urging the two governments to send instantly to Germany a group of newspaper editors and representative groups from the national legislatures. I felt that the evidence should be immediately placed before the American and British publics in a fashion that would leave no room for cynical doubt". General Patton, said to be the toughest man in the entire Third Army, threw up. But Ohrdruf was just the tip of the iceberg - it would be nothing compared to the horror and scale of Bergen-Belsen, Treblinka, Auschwitz and others. Lee Miller would be among the photographers, and the experience would damage her psychologically for the rest of her days - her assignments included two of the very worst - Buchenwald and Dachau.

Lee took thousands of photographs. Jacques Hindermeier, a French Army doctor, was shocked to see a woman taking pictures at Dachau. Decades later he reminisced, "She took the photos I could not take". Fellow photographer David Scherman later observed, "She

never stopped to think about what she was seeing; the shock went underground". Scherman was right. Lee approached her task with cool headed professionalism, gone was the reckless sense of adventure and exhilaration. The shock did indeed however go "underground". It was about this time that her drinking became heavy, and this problem would remain with her for the rest of her life compounded by what would today be diagnosed as "post traumatic stress disorder".

Lee tried to erase the nightmare visions of the concentration camps from her mind with her work in Paris recording the celebrations as well as the dramatic link up of American and Russian troops on the banks of the Elbe River, where large numbers of German troops had rushed to the American lines to surrender in desperate attempts to avoid having to surrender to the Russians. She recorded American GIs embracing Russian soldiers. Lee herself was an enormous hit with the Russian troops, many wanting their photograph taken with her. The Russian army, unlike the American did not lack for women soldiers. Lee indeed was a hit with the Russian women as well. Both sides took part in ritual exchanges of gifts; Russian black bread and onions for American K rations, endless toasts with toxic Russian vodka and German wines. Lee was taken aside by the Russian women, who apparently were more interested in the "engineering" of her French underwear. Lee was more than happy to demonstrate, but remarked later that her "entire "ideological" exchange with the Russians suffered a language impediment due to new methods of drinking vodka". (The Russian women sculled more fiercely than anyone!) By the war's end though Lee remained haunted by what she had witnessed at Buchenwald and Dachau. No matter how intense the victory celebrations they could not ease the horrific images in her mind. In Munich for the final German surrender, Lee felt compelled to visit the home of Adolf Hitler, to try and understand the architect of Dachau which she had visited that morning. When the group entered the bathroom she shocked everyone by stripping naked and taking a bath in Hitler's bathtub. David Scherman recoded the moment and it remains as one of the most famous and enduring images of Lee Miller's time as a war correspondent. She later explained that she had become so agitated she simply had to "wash off the dirt of Dachau". Her face is expressionless, perhaps emotionally conflicted. she poignantly stares back at a sculpture of a female nude, which in turn stares back at the image of the Fuhrer at the foot of the bath. She seems in turmoil. As a blue-eyed blonde, she certainly met Hitler's standards of the Aryan Venus. It was an image she knew well. In her younger years she was the very model for such works. She is torn in the knowledge that she is also the very model of the Nazi idyll.

Lee Miller had always felt that her true potential had not been realized. Spending years as a model to be photographed, she longed to spend more meaningful time on the other side of the lens where she could use her creativity. Eventually she was able to achieve this, but even so, much of her work seemed so routine and repetitive. She still wasn't satisfied, if only the right opportunity came along. It did so - in the form of the Second World War. She would finally use her photography to make a truly meaningful contribution on the biggest stage of all

After years of routine and mundane service in the field of seizure prevention, the agent Levetiracetam, like Lee Miller in 1939, is perhaps poised to make a major new contribution on the biggest stage of Neurology - status epilepticus - and its field of battle operations will now be the Emergency Department!

LEVETIRACETAM (KEPPRA)

Introduction

Levetiracetam (pronounced Leva - ty - raci - tam) (trade name in Australia, “**Keppra**”) is a broad spectrum anticonvulsant.

It is used both as monotherapy and as adjunctive therapy in the prevention of various forms of epilepsy.

Levetiracetam appears to be particularly effective for partial and non-convulsive forms of epilepsy.

Although its efficacy is equal to phenytoin, in status epilepticus, levetiracetam is being increasingly used as a first choice, second line agent (after benzodiazepines) in cases of both convulsive and non-convulsive status epilepticus, with phenytoin being relegated to third line treatment.

Although the two agents seem to be of equal efficacy as second line agents, levetiracetam is being favoured by many due to:

- **Its superior safety profile (predominantly CVS safety profile)**
- **Its ease of drawing up**
- **It's much quicker rate of delivery (over just 5 minutes)**

See also separate document on Anticonvulsant (Newer Agents) Overdose (in Toxicology folder).

History

Levetiracetam was introduced into clinical practice in the United States on November, 2008.

Chemistry

Levetiracetam belongs to a class of chemical known as **racetams** which share a pyrrolidone nucleus

Levetiracetam is a pure enantiomer.

It is the S-enantiomer of etiracetam.

Classification

There is no general consensus on the classification of anticonvulsant drugs, in part due to the wide structural variation as well as the wide variation in the mechanisms of actions of these agents.

The precise mechanisms of action of the non-barbiturate and non-benzodiazepines agents are imperfectly understood.

Many agents probably have more than one action, and individual specific actions can overlap between agents.

In the broadest terms modern anticonvulsant agents can be divided into the barbiturates, the benzodiazepines and other agents.

1. **Barbiturates:**

The principally used agents are:

- Phenobarbitone
- Primidone

2. **Benzodiazepines:**

The principally used agents are:

- Diazepam
- Midazolam
- Clonazepam

3. **Other antiepileptics:**

These agents include:

- | | |
|------------------------|--------------|
| ● Carbamazepine | ● Perampanel |
| ● Ethosuximide | ● Pregabalin |
| ● Gabapentin | ● Sulthiame |
| ● Lacosamide | ● Tiagabine |
| ● Lamotrigine | ● Topiramate |
| ● Levetiracetam | ● Valproate |
| ● Oxcarbazepine | ● Vigabatrin |
| ● Phenytoin | ● Zonisamide |

Preparation

Levetiracetam as:

Tablets:

- **250 mg, 500 mg, 1000 mg.**

Oral liquid:

- **100 mg/mL, 300 mL.**

Ampoules:

- **500 mg in 5 mL ampoule (i.e 100 mg/mL)**



The commonly used 500 mg vial (in 5 mls)

Solution for Infusion:

- **500 mg in 100 mls (i.e 5 mg/mL)**
- **1 gram (= 1000 mg) in 100 mLs (i.e 10 mg/mL)**
- **1.5 grams (= 1500 mg) 100 mLs (i.e 15 mg/mL)**

Mechanism of Action

The precise mechanism of action by which levetiracetam acts as an anticonvulsant is unknown, but it appears to be unrelated to any of the mechanisms of current antiepileptic drugs.

In vitro studies show that levetiracetam affects intra-neuronal calcium levels by binding to a synaptic vesicle glycoprotein, known as **SV2A**.

This results in a partial inhibition of N-type calcium currents and reduces the release of calcium from intra-neuronal stores.

This in turn alters (dampens) neurotransmission.

Pharmacodynamics

Levetiracetam has a broad spectrum of anticonvulsant activity, and is effective for both **partial** and **generalized** seizures.

It is used both as monotherapy and as adjunctive therapy.

It appears to be particularly effective for partial and non-convulsive forms of epilepsy.

It has an emerging role as a second line agent for both convulsive and non-convulsive status epilepticus.

Pharmacokinetics

Absorption:

- Levetiracetam can be given orally or IV.

Levetiracetam is rapidly absorbed after oral administration.

Oral bioavailability is close to 100 %.

- Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight.

In general therefore there is no routine need for plasma level monitoring of levetiracetam.³

Distribution:

- The volume of distribution of levetiracetam is approximately 0.5 - 0.7 L/kg, a value close to the volume of distribution of intracellular and extracellular water.
- Neither levetiracetam nor its major metabolite are significantly bound to plasma proteins (< 10 %).
- Levetiracetam can cross the human placenta.
- Levetiracetam is excreted into human breast milk in small amounts.

Metabolism and excretion:

- Levetiracetam is metabolized in the liver and the metabolites are then excreted in the urine.

Urinary excretion accounts for about 95% of the drug and its inactive metabolites, and dose reduction is recommended in moderate to severe renal failure (GFR less than 50 mL/min).¹

- Levetiracetam does not appear to have any clinically significant drug interactions as it does not induce or inhibit hepatic enzymes and is not metabolized by the cytochrome P450 system.¹

Indications

Levetiracetam appears to be particularly effective for partial and non-convulsive forms of epilepsy.

Indications include:²

1. Monotherapy:

- Of partial (i.e focal) seizures with or without secondary generalisation

2. Adjunctive therapy of:

- Partial (focal) seizures with or without secondary generalisation
- Primary generalized tonic-clonic seizures in idiopathic generalized epilepsy
- Myoclonic seizures in juvenile myoclonic epilepsy in patients > 12 years

3. Status epilepticus:

- **Levetiracetam also appears to be useful as a second line agent in cases of both convulsive non-convulsive status epilepticus.**

Though an effective antiepileptic drug for status epilepticus, its efficacy also depends on the timing of its administration, being more effective when used as **early**.

- **Although its efficacy is equal to phenytoin, in status epilepticus, levetiracetam is being increasingly used as a first choice, second line agent (after benzodiazepines) in cases of both convulsive and non-convulsive status epilepticus, with phenytoin being relegated to third line treatment.**

Although the two agents seem to be of equal efficacy as second line agents, levetiracetam is being favoured by many due to:

- ♥ **Its superior safety profile (predominantly CVS safety profile)**
- ♥ **Its ease of drawing up**
- ♥ **It's much quicker rate of delivery (over just 5 minutes)**

Contra-indications/precautions

These include:

1. Learning disability or history of psychiatric problems:
 - Appears to have an increased risk of behavioral / neuropsychiatric adverse effects.
2. Treatment with drugs that lower the seizure threshold:
 - Use these combinations cautiously, if at all.
3. Renal impairment:
 - Dose reduction is recommended in moderate to severe renal failure (GFR less than 50 mL/min).¹

Pregnancy

Levetiracetam is classified as a category B3 drug with respect to pregnancy.

Category B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans

From the limited safety information available, levetiracetam use in early pregnancy has not been associated with an increased risk of congenital malformations.

However, a combination of levetiracetam with other antiepileptic medicines may increase the risk of congenital malformations.

The decision to treat should be made on an individual basis by considering the risks and benefits to both mother and fetus. Consultation with a neurologist for further advice is recommended.

Women of childbearing potential treated with levetiracetam should take folic acid 5 mg per day, for at least 1 month prior to conception and continue for 12 weeks after conception to minimize the risk of neural tube defects.

Due to changes in levetiracetam disposition during pregnancy, monitor levetiracetam plasma concentrations and adjust the dose as required, especially after delivery, to ensure adequate seizure control.

A small study has shown children exposed to levetiracetam in utero are not at an increased risk of delayed early cognitive development at an age of 24 months or less.

Breast feeding:

There is limited safety information available following the use of levetiracetam during breastfeeding.

Small amounts of levetiracetam are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

If levetiracetam is the medicine of choice, use the lowest effective dose during breastfeeding and observe the breastfed infant for potential adverse effects such as drowsiness, irritability, poor feeding and restlessness.

Adverse Effects

These include:

1. Mild sedation:
 - Potentiated by alcohol.
2. Asthenia (i.e lethargy/ malaise)
3. Insomnia
4. Amnesia
5. Non-specific neuropsychiatric disturbances:
 - Emotional lability
 - Anxiety
 - Aggression/ irritability/ agitation
 - Worsening of depression:
 - ♥ Monitor for suicidal ideation.
6. Allergic reactions.

7. Dermatological hypersensitivity reactions, (rare):

- These may include serious reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Dosing

Exact dosing will depend on the nature and severity of the condition being treated.

Use in the ED should be guided by a Neurologist.

In general terms:

Oral:

Monotherapy:²

Age >16 years:

- Initially 250 mg twice daily for 2 weeks,

Then

- Increase to 500 mg twice daily;

Then

- Increase dose according to response by 250 mg twice daily every 2 weeks, up to **1.5 grams twice daily.**

Adjunctive therapy:

- *Adult, child >50 kg*, initially 500 mg twice daily

Then

- Increase dose according to response, by 500 mg twice daily every 2 - 4 weeks, up to 1.5 grams twice daily.

4–17 years and <50 kg, initially 10 mg/kg twice daily; then increase dose according to response, by 10 mg/kg twice daily every 2 weeks, up to a maximum dose of 30 mg/kg twice daily.

Monitoring with oral dosing:

- Due to its **complete** and **linear absorption**, plasma levels can be reliably predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore plasma level monitoring of levetiracetam is not usually performed.

IV:

In general the dose is the same for oral and IV administration.

A precipitate may occur if intravenous levetiracetam is *mixed* with **phenytoin**, so intravenous lines should be flushed with the appropriate diluent if concurrent intravenous doses are to be given. ¹

Status epilepticus:

Dosing for status epilepticus in two important recent trials (ConSEPT) and (EcLiPSE) as well as the current recommendation from the Monash Children's Hospital Paediatric Emergency Medicine Medication Book, (2nd ed) is as follows:

- **Levetiracetam 40 / kg IV given over 5 minutes**

Using the 500 mg vials (in 5 mls) - dilute each vial used to 10 mls (*Monash Children's Medication Book*)

The maximum dose is **3 grams**.

For patients who are known to be already taking Levetiracetam, some expert opinion suggests using a dose of

- Levetiracetam **20 / kg IV** given over 5 minutes



Lee Miller observing street fighting protected by GIs of General Patton's Third Army at St Malo France, 1944.



Above: Lee Miller by Life Magazine, 1945. Below Left: Lee reunited with Pablo Picasso, Paris 1944. Below Right: Lee with a Russian Commander on the Elbe, 1945.



Silver gelatin black and white photographs by Man Ray, c.1930, and a sculpture found in Hitler's bathroom in Munich 1945. Lee fitted the image of the of the Aryan idyll.

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