# ke0 in Target Controlled Infusion

**$ke_0$ in Target Controlled Infusion**

Pharmacodynamics, Effect-Site Equilibration, and the Eleveld Model

Don Macalister Consultancy | TCI Education Series

## What is $ke_0$?

In the context of Target Controlled Infusion (TCI), $ke_0$ (pronounced “kay-zero”) is one of the most important pharmacodynamic concepts to understand. It links the pharmacokinetics (where the drug is) with the pharmacodynamics (what the drug is doing).

$ke_0$ is the first-order rate constant describing how quickly a drug equilibrates between the plasma and its effect site — usually the brain for hypnotics and opioids.

In other words:

- The TCI pump knows the plasma concentration (Cp).
- The patient responds to the effect-site concentration (Ce).
- $ke_0$ determines how fast Ce catches up with Cp.

## Why Does it Matter?

Imagine giving a bolus of propofol.

### Immediately after injection:

- Plasma concentration rises very rapidly.
- The brain concentration is still increasing.
- The patient is not yet at maximum hypnotic effect.

### Over the next minute or two:

- Propofol diffuses into the brain.

- Effect-site concentration increases.
- The patient eventually reaches peak hypnosis.

*Without accounting for $ke_0$, you would falsely assume the patient should already be asleep simply because the plasma concentration is high.*

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## Visual Analogy — The Sink

Think of filling a sink:

- The tap = plasma
- The water in the basin = effect site

The tap can be turned on instantly. The basin takes time to fill. The speed at which the basin fills is governed by $ke_0$.

## Large vs Small $ke_0$

| | | |
|---|---|---|
| **Large $ke_0$**<br>• Rapid equilibration<br>• Faster onset<br>• Plasma and brain concentrations become equal quickly | | **Small $ke_0$**<br>• Slower equilibration<br>• Delayed onset<br>• Greater lag between plasma and effect-site concentrations |

## Relationship to Effect-Site TCI

Modern TCI pumps target:

- Effect-site concentration (Ce)

*When targeting Ce, the pump deliberately overshoots the plasma concentration initially so that the predicted brain concentration reaches the requested target as quickly as possible without excessive overshoot. This is why effect-site targeting generally provides a faster, smoother induction than plasma targeting.*

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## $ke_0$ Versus $t_{½}ke_0$

Many clinicians find the effect-site equilibration half-time ($t_{½ke_0}$) easier to understand.

The relationship is: $t_{½ke_0} = 0.693 / ke_0$

So:

- Higher $ke_0$ → shorter equilibration half-time
- Lower $ke_0$ → longer equilibration half-time

## Typical Values

Approximate values reported in adults include:

| Drug | Peak Effect | Approximate $t_{½ke_0}$ |
|---|---|---|
| **Propofol** | 90–100 s | ~1.7 min |
| **Remifentanil** | ~1.8 min | ~3.0 min |
| **Fentanyl** | ~3.6 min | ~4.7 min |
| **Midazolam** | ~2.8 min | ~4.0 min |

## How This Relates to the Schnider Model

The Schnider propofol model incorporates a $ke_0$ chosen to allow reliable prediction of effect-site concentrations. Because of this, most clinicians performing procedural sedation with TCI prefer effect-site targeting using the Schnider model, as the displayed Ce correlates more closely with the patient's clinical level of hypnosis than the plasma concentration does.

## Clinical Takeaway for TCI Sedation

*When you increase the target from, for example, Ce 1.5 to 2.0 µg/mL, the patient will not become maximally sedated immediately. The brain concentration requires time to equilibrate with the plasma concentration according to the drug's $ke_0$. This is why experienced TCI practitioners increase targets incrementally and wait for equilibration before making further adjustments.*

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**$ke_0$ and the Eleveld Model**

How $ke_0$ Differs Across Marsh, Schnider, and Eleveld — and Why it Matters Clinically

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For TCI practitioners, one of the biggest advances of the Eleveld pharmacokinetic model is that it re-examines how $ke_0$ is estimated and uses a unified model across a much wider range of patients than older models such as Marsh and Schnider.

## Model Comparison

| Feature | Marsh | Schnider | Eleveld |
|---|---|---|---|
| **Primary population** | Healthy adults | Adults | Neonates to elderly, healthy and many disease states |
| **Effect-site targeting** | Added later | Integral to model | Integral to model |
| **$ke_0$** | Fixed | Fixed | Estimated within a unified PK/PD model |
| **Weight handling** | Total body weight | Lean body mass | Body size + age, comprehensively |
| **Typical use** | Older TCI pumps | Most procedural sedation | Newer generation TCI systems |

## The $ke_0$ Differences

The key point is not simply that Eleveld uses a different $ke_0$ number.

*Eleveld re-estimated the entire pharmacokinetic/pharmacodynamic system from tens of thousands of concentration measurements across a very diverse population. The $ke_0$ value therefore works together with different compartment volumes and clearances. This means you cannot meaningfully compare the $ke_0$ values between models in isolation, because each $ke_0$ is only valid within its own pharmacokinetic framework.*

## Clinical Impact

### With Schnider:

- Ce usually rises rapidly.
- The initial plasma overshoot is moderate.
- Induction is familiar to most TCI users.

### With Eleveld:

- The predicted plasma concentration needed to achieve a given Ce is often different.
- The Ce rise is smoother in many patients.
- The model adapts more realistically across extremes of age and body size.
- Predictions tend to be more consistent when treating obese, elderly, or paediatric patients.

## A Practical Example

Suppose you target Ce = 2.0 µg/mL.

### Using Schnider, the pump might:

- Deliver a relatively brisk loading infusion.
- Reach the target Ce in about 90–120 seconds.

### Using Eleveld, the pump may:

- Use a different loading profile.
- Display a different plasma concentration while reaching the same Ce.
- Produce a slightly smoother approach to the target.

*The patient still reaches a predicted Ce of 2.0 µg/mL, but the route taken is different because the pharmacokinetic model is different.*

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## Why Many Anaesthetists Are Interested in Eleveld

The Eleveld model attempts to overcome recognised limitations of earlier models:

- Marsh performs less well in obesity and elderly patients.

- Schnider relies on lean body mass equations that can produce implausible values in some obese individuals.
- Neither was developed from children through to very elderly adults.

## Does This Make Induction Safer?

The evidence so far suggests a more nuanced answer.

### Potential advantages:

- Better prediction across a wider range of patients.
- Less need to switch models based on patient characteristics.
- Improved prediction of propofol concentrations in populations underrepresented in older models.

### What has not been conclusively demonstrated:

- Superior clinical outcomes in routine adult procedural sedation.
- Lower rates of hypotension, hypoxia, or oversedation solely because Eleveld is used.
- Universal superiority over Schnider in healthy adults.

*Better prediction does not automatically translate into better clinical outcomes, because operator skill, patient variability, monitoring, and titration remain major determinants of safety.*

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