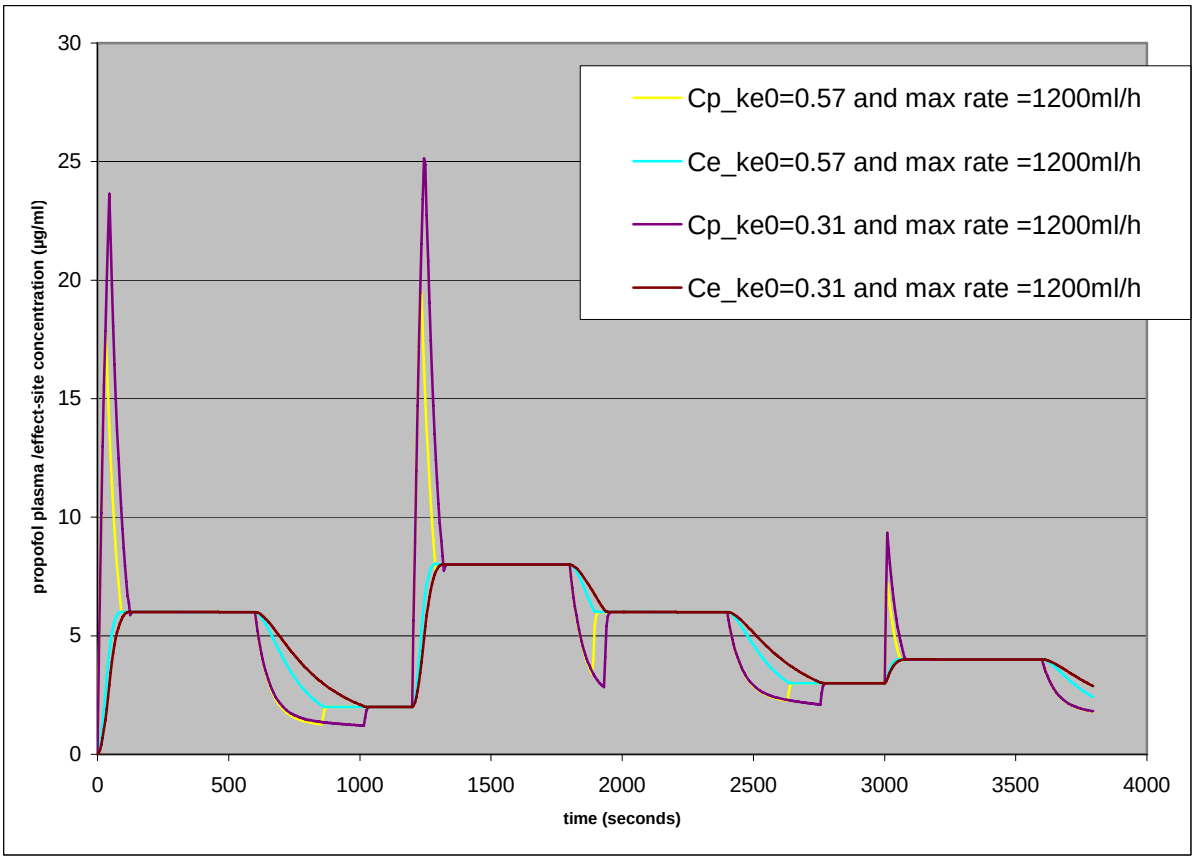
Appendix 2, Web Enhancement : Simulations showing the influence of the k_{e0} on the actual infused amount of propofol over time when using a target controlled infusion system.

We have simulated the following population :

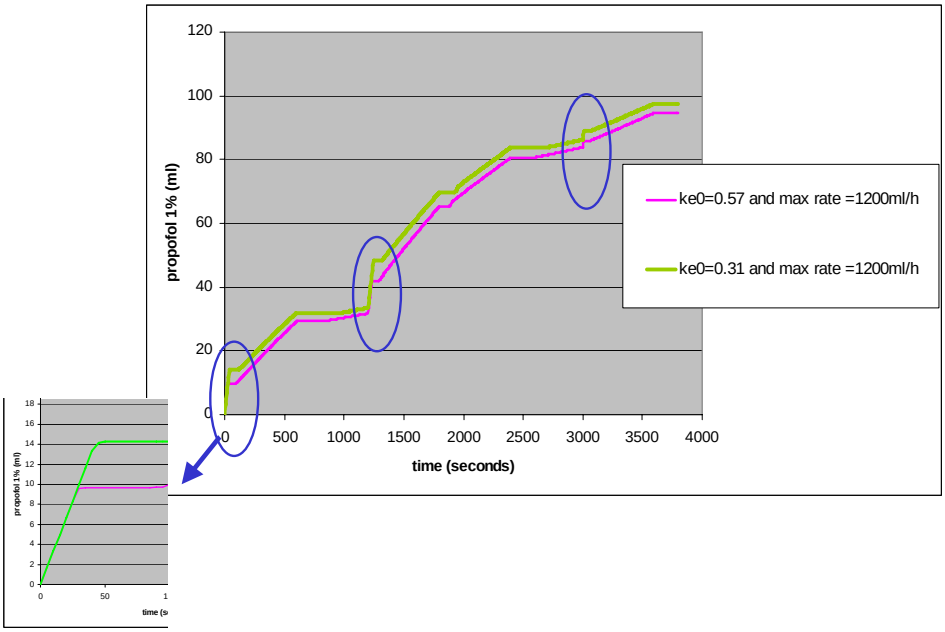
patient	weight	Length	age
1	75	163	26
2	62	168	42
3	63	163	32
4	87	181	32
5	88	170	38
6	53	168	32
7	65	165	32
8	65	174	32
9	52	163	42
10	52	163	30
11	48	156	29
12	74	180	43
13	62	172	35
14	70	180	33
15	65	169	39
16	61	168	35

We have developed a target controlled infusion system with the model of Schnider for the kinetic part and a ke0 of 0.57 and 0.31 as in the study. We have simulated a target controlled infusion of several steps up and down as seen in the figure below (revealing the mean profiles for the population) :



Cp means predicted propofol plasma concentration, Ce means propofol predicted effect-site concentration and ke0 is the plasma-effect-site concentration first order equilibration constant.

With a classical maximum infusion rate of 1200 ml/h (for standard target controlled infusion pumps), a different ke0 makes a difference. The smaller the ke0, the bigger the peak plasma concentration. As such, a smaller ke0 will lead to a higher peak. This will also result in a difference in amount of propofol used, specifically during the increases in target effect-site concentration. The figure below shows the mean population cummulative volumes given during the above mentioned target controlled infusions.



It is clear that the ke0 of 0.31 results in more propofol injection at increasing target concentration. In previous work (Struys et al., *Anesthesiology* 2000; **92**: 399-406), we have already shown that a too large overshoot in Cp during effect compartment target controlled infusion lead to a more pronounced hemodynamic depression.

Next to the above mentioned implementation, the reviewer should know that our work should be seen in the context of the longlasting discussion in the "target controlled infusion community" which model for propofol is right. The Diprifusor® (AstraZeneca, London, UK) one using a slower ke0 or the Schnider model using a faster one. The "Schnider" believers state that "Marsh" is wrong and visa versa. With this work, we want to prove that nearly all models published on propofol are right and probably influenced by the method of drug administration. That's the mean issue in this work…and as such, has a very important clinical implementation. Please, realise that even for the commercial target controlled infusion pumps available in Europe, companies are asking what is the right model to implement…