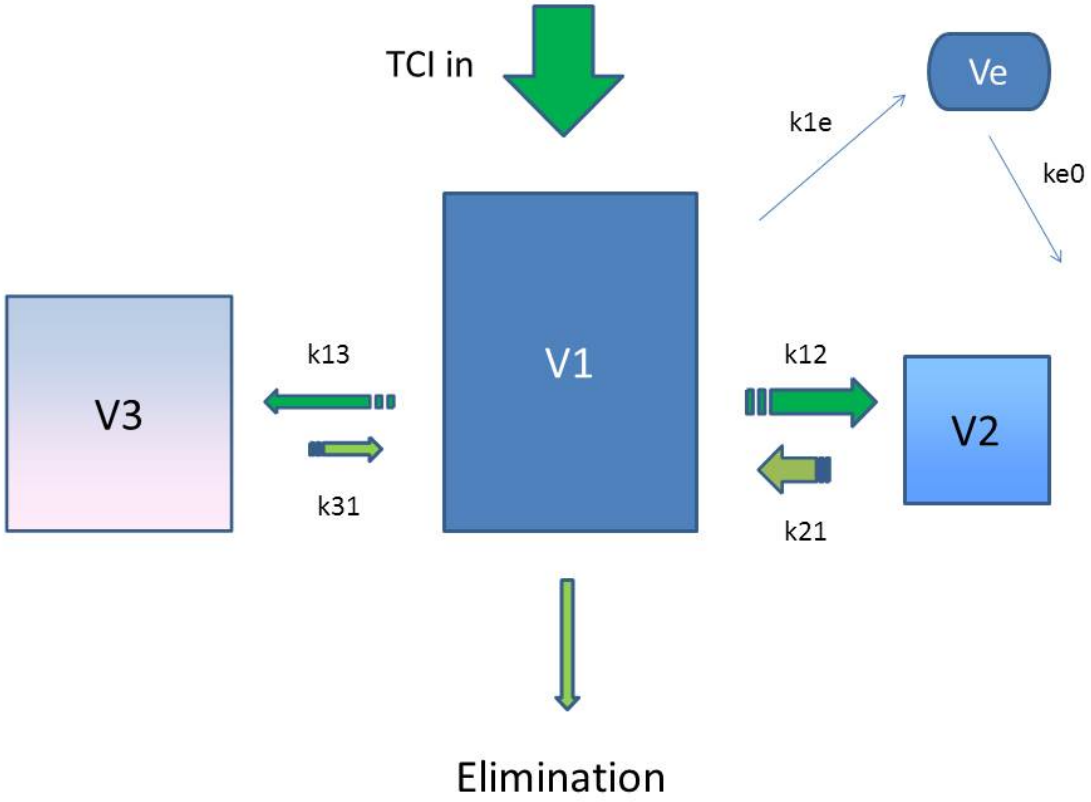
Behind the scenes in TIVA pumps

There is clearly a vast amount of processing of information going on in TIVA pumps in order to deliver what we consider to be the correct amount of drug to a patient. The pumps know the age, height weight and sex of the patient and they use some or all of this information to calculate what initial bolus of drug is required and what maintenance should be infused to allow a steady state of drug to remain at the effect site.

To complicate rather than simplify matters, there are differences in how different pump manufacturers handle the various algorithms available for an individual drug and the algorithms themselves also differ in how they interpret the 3 compartment model, shown below –



The one fact that can conveniently excuse the difference between the Marsh and Schneider propofol models is that Marsh was designed for plasma targeting, whilst Schneider was designed for effect site targeting. We could conclude that for propofol therefore we should use Schneider when targeting to effect site and Marsh if targeting to plasma. Both will give a gentle induction with more cardiovascular stability. Indeed, some manufacturers do not allow the choice of Marsh with effect site targeting. However, given that Minto (the sole algorithm for remifentanil) can always be chosen for effect site or plasma targeting, we would have the scenario where we may be targeting one drug to plasma and one to effect site, which appears somewhat illogical in an individual patient. It doesn't actually matter as each algorithm will give a controlled and safe amount of drug. It is just that when targeting

to effect site, the pump will give a bolus of drug to maximise (safely) the concentration gradient between V1 and the effect site to promote more rapid equilibration of the drug. This will inevitably result in a higher peak plasma level than when targeting to plasma, when the plasma level will by definition not exceed the level chosen. This means that the concentration gradient (along K1e) will be smaller and so equilibration between V1 and Ve will take longer. The peak plasma level of effect site targeting may be substantially higher than the chosen target level and it is this peak level which causes a *pharmacodynamic*hit in terms of cardiovascular compromise resulting principally in hypotension.

There is, as you might expect, another factor that affects what algorithm we choose and possibly in which patients! The fundamental value of the volume of the central compartment into which the drug is injected for distribution (V1) is different in each algorithm. In a patient of 70Kg, this is some 16 litres in the Marsh algorithm whereas it is only 4 litres in the Schnider algorithm. So immediately one can see a sizeable difference in dose of drug injected at the outset, to satisfy the algorithms' requirements according to calculated differences in V1. This explains why (from what has been previously explained) Marsh at effect site will result in a big pharmacodynamic hit whilst Schnider at plasma will barely induce unconsciousness at all.

The use of the Schnider algorithm (effect site) may therefore appear attractive in ASA 3 4 and 5 patients combined with remifentanil (Minto) at plasma targeting. The latter setting reflecting the undesirability of having the pharmacodynamic hit of any drug targeted to effect site. In purist terms, this is a perfectly reasonable argument. However what do you use for the converse, ASA 1 and 2 patients, in whom a pharmacodynamic hit is not considered such an undesirable phenomenon? After all, when 20 mls of 1% propofol is administered manually from a syringe to a patient, a dose far in excess in comparison to a programmed TIVA pump is given and at a rate in excess of 1200 mls/hr which is the usual bolus rate set on the pumps. ASA 1 and 2 patients show themselves to become anaesthetised safely and swiftly when effect site targeting is chosen for Minto (remifentanil) and Marsh (propofol). In this way, both drugs are set to target the same site. For the converse, ASA 3 4 and 5 patients, again Marsh and Minto can be used but both set to target plasma instead, thereby avoiding a "peak plasma level" and a pharmacodynamic hit. Arguably, there is less margin for error than changing algorithms for propofol and sites for remifentanil in more frail patients. However, despite the attempts to keep matters simple, it should be borne in mind that the Schniderpropofol algorithm was designed with effect site targeting in mind, whereas Marsh (as per the Diprifusor with pre filled syringes of propofol) was designed for plasma targeting. Nonetheless Marsh can be safely used for effect site targeting in the ASA 1 and 2 population. Conversely, Schnider in plasma mode will "fail" to induce anaesthesia.

So now let us consider what patient demographics are used in the algorithms to calculate the dosages administered. Marsh simply uses weight. You have to factor in age and co-morbidity / concurrent drug therapy. Marsh does use age, but only to lock out the algorithm if the age is entered as being less than 16 years old. Schnider and Minto however use all 4 parameters. Height and weight are combined to ascertain lean body mass, using the James equation, rather than simple body mass index. Herein lies a problem – obesity.

Obesity is a familiar dilemma; we are used to adjusting drug dosages of many kinds of drugs especially muscle relaxants according to our own preferred "formulae" for ideal body weight for height. The James equation referred to is a quadratic equation, resulting in a plot similar to a Frank-Starling curve for myocardial contractility against PCWP. There is an optimal point, after which an increase in PCWP results in a decrease in myocardial contractility. In a similar manner, at a point of weight (different in males and females), the lean body mass component of that weight, will start to fall as weight increases. At this point, both Schneider (propofol) and Minto (remifentanil) models will start to *reduce the amount of respective drug given*as weight increases. Theoretically therefore at a very high body weight, no drug at all will be delivered! Clearly this is silly and something must be done to counteract this phenomenon. Two manufacturers have a different approach to the problem. Fresenius' Base Primea pumps will simply not allow targeting on the algorithms using the James equation (Schnider and Minto) if a male BMI is over 42 or a female is over 35. They use BMI to reflect body weight. On the other hand, Care Fusion's Alaris PKpumps, follow the theoretical curve of LBM vs weight and when it peaks at a maximal drug dosage for men and for women, it assumes that this is the maximum LBM to be allowed and calculates drug dosage on this basis, allowing targeting with Schnider and Minto algorithms. As Marsh is based only on weight, it allows targeting (at either site) in the usual manner. A number of different alterations have been tried to allow the Fresenius Base Primea pumps to work by altering a specific patient parameter, but such programming is not yet recognised as being appropriate and so will not be discussed further here.

In addition to the above algorithm differences, are manufacturer differences in how the algorithms are "used" to calculate drug dosage delivery. One particular difference is with the old chestnut of the Ke0 value. The Base Primea system keeps a fixed Ke0 appropriate to each drug, whilst the Alaris pumps calculate a different Ke0 for each patient! This appears quite a radical difference in calculating drug administration and indeed it is, but it is probably best considered as viewing it as a sum with one fixed component and an answer. For example the answer is 18 and a fixed component is 9, so the sum could be 9 x 2 = 18 0r 16 + 2 = 18, or 3 x 6 = 18. It is the same thing with the same answer expressed in different ways. The important fact is that both calculations work and have worked reproducibly over very many cases.

Other differences in algorithms are assumptions concerning the variables and the fixed parameters – rate constants vs age, elimination rates vs age and they are varied by algorithm in order to make "the equation" or the calculated doses, "correct" or effective. The precise factors defining the mls per hour of drug delivered by each pump are down to the *algorithm* chosen rather than the pump manufacturer, except for the Ke0 differences referred to previously. What these differences are, are beyond the scope of this resume as that involves dissecting the algorithm and analysing its constituent parts.

What we can be clear upon are the basic measurements made to define how each drug appears to behave in a 3 compartment model. Put simply, a known bolus of a drug is administered to a person and arterial and venous measurements are made at repeated frequent intervals. In addition, the effect of the drug is measured against time – the effect of propofol on Bispectral Index (BIS) against time can be plotted to show reproducibly that the time to peak effect (TPE) is 100 seconds. If this is then repeated in patients of different sexes, different ages, different lean body masses……it can be seen that after a number of

combinations of analyses, trends can be spotted that guide the mathematical relationship between drug administration, its effect and its eventual elimination - this, is the world of PK/PD modelling! It is therefore no wonder that we can arrive at the answer of 18 by 9+9, or 3 x 6, or 2 x 9, or 17 + 1….

NJHuggins Feb 2015