Extended Abstract

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Comparison Between Remifentanil Blood, Cerebro-Spinal Fluid and Cerebral Extracellular Fluid Levels and Tci Prediction: A Pharmacokinetic Study

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Abstract: Remifentanil is a synthetic opioid, characterized by quick onset and similarly rapid offset, the latter being a result of its large clearance by plasma and tissue esterases. These characteristics make remifentanil ideally suited for target-controlled infusions (TCI). Consequently, Minto developed a pharmacokinetic model which allows its administration via a TCI infusion system. (1,2,3) In 2003, Mertens demonstrated that the pharmacokinetic parameter set described by Minto resulted in significant median over prediction of the measured plasmatic remifentanil concentration by 15% with an inaccuracy of 20%. The conclusion from his study was that "remifentanil can be administered by TCI with acceptable bias and inaccuracy". (4)

In the same year, Hoymork concluded his study showing that TCI for propofol and remifentanil gives large variations in measured serum values, with a significant median over prediction of 25%. Despite huge variations in measured concentrations of propofol and remifentanil, almost all patients in his study experienced uneventful anaesthesia. (5)

In spite of these studies, so far the cerebral concentrations of the drug have never been verified in vivo. Even though we are well aware of the fact that the effect site as described in the pharmacokinetic model cannot be directly measured within the brain being a virtual compartment with no capacity by definition, the premise for our study was that knowing the blood/brain ratio of remifentanil concentration would be useful to add information on the actual behaviour of remifentanil in a living organism.

The first end-point of the study is to elucidate further the difference in concentration between these compartments, the second one is to verify the presumable existence of a correlation between arterial and cerebral remifentanil under stable conditions. Brain microdialysis has been used to shed light on this aspect of the pharmacokinetic and to correlate these findings with Minto's model.

Background: In order to explain the difference in the concentration among remifentanil blood level, cerebral extracellular fluid level and the cerebrospinal fluid, and also to verify the presumable existence of correlation between the cerebral and arterial remifentanil. Brain micro dialysis was used in order to correlate these findings with Minto's model and to shed light on this aspect of the pharmacokinetic.

Methods: The study population was formed by patients scheduled for elective intracranial surgery for cerebral supratentorial neoplasia. On the whole, nine patients were enrolled to the study. All patients received general anaesthetic. 100 microliters of dialysate were collected. Furthermore, arterial blood samples of 3 ml each were collected, respectively one at the beginning and one at the end of the sampling period. The concentration was determined of remifentanil and its metabolite, remifentanil acid, in the blood and brain. By examining the performance error the predictive performance of the Minto pharmacokinetic parameter set was evaluated.

Data analysis: Data regarding measured concentration values recorded in an Excel spread sheet; statistical calculations were performed with the statistical package Medcalc. The Student's T-Test for pair samples has been used to compare the two series of arterial samples. The predictive performance of the Minto pharmacokinetic parameter set was evaluated by examining the performance error. For each sample the PE was calculated as PE % = [(Cm-Cp)/Cp] x 100, where Cp is the predicted concentration in the compartment in question, while Cm is the measured concentration of remifentanil in that compartment. Median PE for all samples was calculated. Subsequently, Pearson's correlation coefficient was calculated between the predicted value and the measured values, as well as between predicted values.

Results: Of the nine patients recruited, one has no interstitial fluid value available because of intra operative catheter damage. Mean age of the patients was 44 (40-50, SD 3.53). Mean height was 170 cm (165-178, DS 4.03) and mean weight 74 kg (70-83, DS 4.23).

All data series resulted to be normally distributed (Kolmogorov-Smirnov test). The concentration of remifentanil does not significantly differ between the two series, whereas remifentanil acid is significantly higher in the second series ($t=4,276$, $p<0.01$). The mean Performance Error was - 45.13% (min -21.80 max -88.75) for the first series of arterial samples, -38.29% (min -6.57 max - 79.17) for the second one and 67.73% (min 7 max -93.12) for the ECF fluid sample. Mean PE of the first series of samples is not significantly different from the one of the second series (Student's t-test). The concentration of remifentanil set on the pump was statistically correlated with the concentration found in the blood for both series of samples (Pearson's bilinear correlation, $r=0.8078$, $p<0.01$ e $r=0.8061$, $p<0.01$ respectively). However, neither the set concentration nor the arterial samples were correlated with the ECF concentration. Also the concentration of remifentanil acid in blood and ECF has no correlation for either of the two series of blood samples. Remifentanil concentration is correlated with the concentration of remifentanil acid in the first series of samples ($r=0.7459$, $p=0.02$), but not in the second. Our two venous samples showed that venous concentration was in both cases lower than the arterial one, as expected.

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Discussion: Our study has shown a valid correlation between predicted and measured blood concentration of remifentanil and an absolute median PE between 38% and 45%. This data contrasts with previous literature that showed an absolute median PE not higher than 15%(4). This poor predictive performance may have been partly caused by the fact that despite being very homogeneous, our population was different from the one from which Minto's algorithm was developed. The latter was in fact rather heterogeneous, in order to gather information on

the different covariates that affect remifentanil pharmacokinetics. Furthermore, in the previous studies the number of samples per individual was higher than two, and the patients were more than 9. Therefore, all these factors may have impaired the accuracy of our data.

As far as cerebral interstitial concentration measurements are concerned, there are some remarks to make. Firstly, the effect site cannot be properly identified with the brain in pharmacological terms, as it actually is a virtual compartment. The brain is an organ, therefore, should be better described as an organ belonging to the fast compartment and follow the kinetics predicted by the constant k12, rather than ke0. If we take a 40-year-old, 70-kg man as an example, Ke0 will be 0.588, while K12 will be 0.39, at about two thirds of the former. As a consequence, it may be expected for the cerebral concentration to take 33% more than the virtual effect site to reach equilibrium with the blood.

Nevertheless, this does not explain the high absolute median PE (67%) or the absence of correlation between the set concentration and the measured ECF concentration. The fact that the remifentanil target was kept constant for all the duration of the sampling should have prevented such a discrepancy. It is important to note that despite the fact that propofol has been reported to be able to alter the kinetics of remifentanil, this seems to occur in a dose-independent fashion (12), and therefore should not account for the variability found in the present study.

Another critical point of our work is the correction factor we applied as a consequence of the results of our in vitro experiment with glucose. Glucose and remifentanil have a different molecular weight (180 v 367 d), therefore it cannot be taken for granted that they will behave in the same way with respect to the semi permeable membrane of the microdialysis catheter. However, Hutchinson et al. (8) showed that glucose and pyruvate share a similar recovery ratio despite the former having a molecular weight twice as large as the latter. In that study, the main factor affecting the recovery ratio was the infusion rate. For these reasons, it is our belief that even in the event of an inaccurate conversion factor being used, this might have explained only partly the inconsistency of our results; especially, it cannot account for the lack of correlation between target and measured concentration.

On the contrary, it is noteworthy to point out that microdialysis only allows to monitor the events happening in a very limited area, and therefore may be influenced by alterations of the local blood supply. Nevertheless the study showed that the Minto parameter set consistently predicts values which are higher than the measured ones, both in blood and in the ECF. This is shown by the negative value of the calculated PE. In particular, PE of the ECF was higher than that of blood, indicating an even more significant over prediction of ECF concentrations. The explanation for this phenomenon may be searched in the intracerebral metabolism of remifentanil, as confirmed by the arterovenous difference in concentration previously reported by other studies . (9) Furthermore, it should be considered that 70% of remifentanil is in the blood in its protein-bound form, but only free remifentanil is able to cross the blood-brain barrier. Lastly, it is possible that the remifentanil that is not bound to opioid receptors is continuously being metabolised by the cerebral tissue esterases, decreasing the unbound fraction in the interstitial fluid.

As to remifentanil acid, its half-life is about nine hours (10), much longer than remifentanil's; therefore, its on average higher value in the second series of samples was an expected finding. This also explains the lack of correlation between remifentanil and its metabolite in the second series of arterial samples. The absence of correlation between cerebral and plasmatic concentrations of remifentanil acid deserves the same considerations already discussed for remifentanil. The difference between arterial and venous blood samples witnesses the importance of tissue clearance in the metabolism of remifentanil, confirming previous data reported by Hermann et al. (11).

Conclusions: We confirmed the presence of wide interindividual variability with regard both to blood and cerebral remifentanil concentration. Moreover, the ratio between arterial blood and cerebral remifentanil was not consistent among our patients in spite of the stable infusion rate of remifentanil ;at the end we found a trend in the ratio between the various compartments examined.

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