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Remifentanil Analgesic Interpatient Variability Assessed Through Pupillary Reflex Dilation

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Background

Although there has been significant focus on neurophysiologic techniques to ensure unconsciousness and amnesia, identifying the neural signatures of effective analgesia has received less attention (Mashour, 2013). Currently, appraisal of intraoperative nociception is mostly done through the assessment of the autonomic response to noxious stimuli, whether it is through heart rate variability, heartbeat intervals, plethysmographic pulse wave amplitude, skin conductance or pupillary response (Edry et al., 2016). The known wide inter-patient variability of the hypnotic effect (3), namely in the amount of propofol needed to achieve loss of consciousness, led us to question if this variability also happened for the hypnotic effect. In this study, we evaluated the interpatient variability of the pupillary reflex dilation response to different levels of remifentanil, administered using target controlled infusion with the Minto Pk Model.

MethodsThis is an observational prospective study, where 34 consecutive patients were enrolled. Patients scheduled for neurosurgical procedures, with general total intravenous anesthesia (using target controlled infusion systems) with propofol and remifentanil were considered when no premedication was used. Induction began with a constant remifentanil concentration using Minto PK Model and then an infusion of propofol at 200 ml/h was started until loss of consciousness was observed. Afterwards, an infrared portable pupillometer (AlgiScan® - IDMed, France) was used to assess the Pupillary Dilation Reflex and its derived index Pupillary Pain Index (PPI). Remifentanil concentrations could be increased if deemed necessary by the anesthesiologist. The PPI results from the pupillary dilation response to a continuously increasing electric stimulus discharge. PPI measurements were taken after loss of consciousness and before surgery, at moments when no other stimulus were present. For each measure of PPI the predicted effect-site concentration (EC) of remifentanil and of propofol (Schnider PK Model); Data are mean±SD or %

Results: 34 consecutive patients were enrolled, and a total of 78 measures of PPI were done. Figure 1 shows the PPI variability for different levels of remifentanil EC and Table 1 shows the PPI values for the four levels of remifentanil. The variability found ranged from 80% to 500%, depending on the effect site concentration of remifentanil. The higher the concentration, the larger the variability. The mean PPI is the difference between the different Remifentanil EC levels (ANOVA $p<0.001$).

Conclusions:We showed that even though there patients received the same anesthetic drugs in fairly similar conditions, they showed variability of the analgesic effect, assessed through the pupillary dilation reflex, as high as 500%. This suggests that more attention should be paid to the individualization of intraoperative analgesia, as different patients have different needs, and these need cannot be predicted only through pharmacokinetic modelling. Further research should be done, with more data and more stratified levels of remifentanil.

1) 10.1097/ALN.0000000000001130

2) 10.1097/ALN.0b013e318279fb40.

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Figure 1

Table 1: PPI values for the different Remifentanil concentration levels.

Remifentanil EC	N	PPI (mean±SD)	PPI (min – max)	PPI – IQ range and %
< 2 ng/ml	21	6.33±2.6	(1 – 9)	[5-9] 80%
2- 3 ng/ml	18	6.11±3	(1- 9)	[2 - 8] 300%
3-4 ng/ml	20	3.7±2.7	(1 – 8)	[1.25 – 1.75] 440%
> 4 ng/ml	19	3.16±2.3	(1 – 7)	[1 - 6] 500%

Figure 2

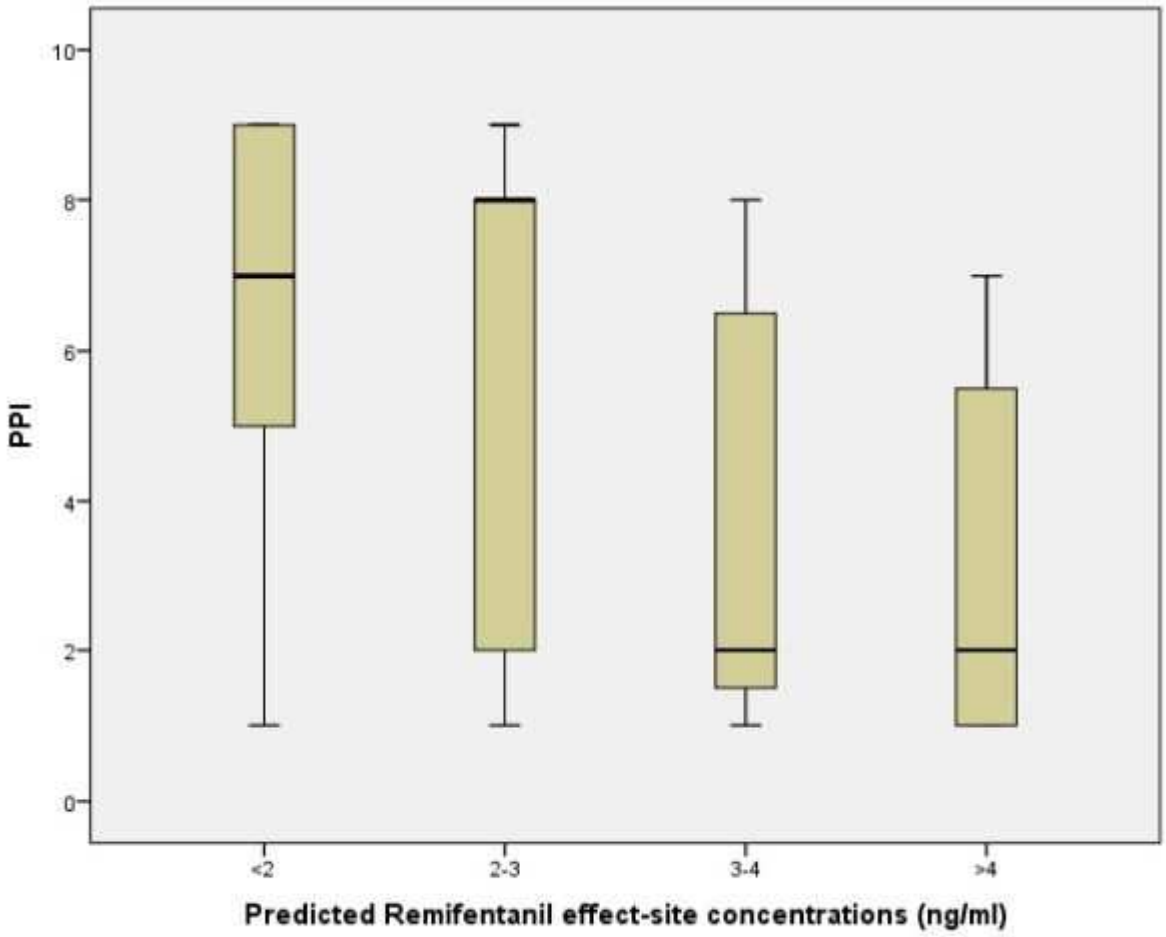

Figure 1: PPI data distribution in the four different remifentanil concentration levels.

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