Pharmacodynamic modelling of pupil diameter after noxious stimulus in patients undergoing surgery

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Introduction:

Movement is an extensively characterised response to noxious stimulus. However, its applicability to assess intraoperative pain has limitations due to the effect of anaesthesia in the response. Previous research has shown that pupil reflex, an indicator of anesthetic depth, could also predict movement after noxious stimuli. The objective of this project is to characterise the effect of remifentanil and propofol on the pupil size over the time course of the operation and to evaluate the pupil size as a predictor of response to movement after anaesthetic and/or nociceptive stimulus enabling anaesthesiologists to optimise dosing during surgery.

Methods:

Patients undergoing gynaecological surgery were recruited for the study. Pupil diameter was measured multiple times before and after surgery using the AlgiScan (Neurolight, IDMED™) hand-held pupillometer which was also used to delivered a 60 mA tetanic stimulus during 5 seconds in the forearm of the patient. Movement response to the stimulus was evaluated in a categorical scale ranging from 0 (absence) to 3 (strong movement) by the physicians. Propofol and remifentanil concentrations in plasma and effect site were predicted using previously validated PK models. Data were analysed using NONMEM 7.4.

Results and discussion:

Eighty-seven female patients participated in the study each having a median of 5 measures of pupil size after noxious stimulation during surgery. The first measure was performed in the presence of propofol and the rest in the presence of propofol and remifentanil. A two-compartment indirect response model accurately described the time course of pupil diameter. In this model, the administration of the tetanic stimulus modulates a nociceptive compartment which subsequently

controls the turnover of the pupil diameter. Remifentanil reduced pupil diameter by modulating the perception of the stimulus and the turnover of the nociceptive compartment. Precision of the parameter was estimated accurately (RSE <40%) although high inter-individual variability was observed. Model performance was based on goodness of fit plots and visual predictive checks.

Conclusions:

A semi-mechanistic pharmacodyamic model to describe the pupil size after a noxious stimulus in the presence of propofol and remifentanil was successfully implemented. This model will be further developed to incorporate the movement response.