CLINICAL PHARMACOLOGY ON DISPLAY

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Monitoring of fundamental physiological variables during anaesthesia is considered essential, but as we develop the ability to monitor more functions, information overload may become a problem. A distributed situation awareness framework is what we need to perceive elements in the environment (detection), comprehend the current situation (diagnosis), and make projections of future status (prediction) [1]. Can smart monitors improve our diagnosis and prediction?

Our mandatory monitors are largely related to respiration and circulation. We can easily and precisely adjust ventilation, but as clinical pharmacologists, do we also have monitors that help us administer drugs? We need to titrate drugs because of the rapidly changing requirements during anaesthesia, and wide individual variability in response. Cardiovascular drugs are usually easy to titrate because we have real-time monitors of heart rate and blood pressure. However anaesthesia drug dosing is somewhat empiric and reactive, sometimes purposely erring on the side of overdosage or underdosage, and sometimes guided by concentrations. Can we develop a real-time display showing the effects of all our anaesthetic drugs? This talk is largely based on my recent editorial with the same title [2].

Neuromuscular Blocking Drugs

We have used peripheral nerve stimulators for many years, although our evaluation of block has often been qualitative, and we have not usually recorded these results. Newer quantitative monitors that display a graphical trend of twitch height depression can show us the time course of drug effect, and modules integrated with anaesthesia workstations centralise the display of neuromuscular block.

Volatile Anaesthetics

These have more than one desirable effect (hypnosis, suppression of somatic responses, suppression of autonomic responses) and the challenge is to find a measure of each effect that can be easily displayed. An early measure of effect is the minimum alveolar concentration (MAC) that is displayed (sometimes uncorrected) on many anaesthetic monitors. MAC is an effective dose (ED50) on the quantal response / no response curve – the concentration at which 50% of subjects do not move. Who wants to give a concentration at which half the patients move? Who knows at what concentration or multiple of MAC would nearly all patients not move? Instead of displaying the concentration as a fraction or multiple of MAC, one could display the effect on the quantile dose-response curve. For example, 2.07% sevoflurane is 1.21 MAC, but this is also the ED95 for no movement. Similarly, if our effect of interest was hypnosis, the concentration could be displayed as an EDx where x% of the population would be expected to not respond to verbal command. MAC and ED values are variables derived from populations that may be very different from the patient currently undergoing anaesthesia. Is it possible to have a measure of anaesthetic drug effect that reflects the individual? Hypnosis is monitored using derived measures of the electroencephalogram (EEG) such as the Bispectral Index (BIS) and Entropy. Although the raw EEG reflects the state of the current patient, the derived indices are also based on models from other populations. The BIS is presented as a number from 0 to 100, and the user is expected to understand what the numbers indicate, as a guide to dosage. The BIS could also be related to the probability of the patient responding to verbal command, but this relationship is not the same for different drugs and drug combinations.

Intravenous Anaesthetics

We can use EEG measures such as the BIS to guide propofol titration with the same limitations as above. It is possible to predict the concentration of propofol but this presumes we know what concentrations are required for the effect that we want. We also need to appreciate the limitations of the pharmacokinetic model being used.

Opioids

For opioids, we usually use a combination of experience and cardiovascular signs to titrate dose. There are programs to calculate the opioid concentration given the dosing history but they are rarely used, even though with them we could potentially target an opioid concentration at the end of anaesthesia with a high probability of analgesia but a low probability of apnoea.

Although it is possible to display the individual measured or predicted drug concentrations, drug interactions among our anaesthetics influence the final effect. Does one need to know the concentrations if one can monitor the effect? We have a good understanding of drug interactions that have been characterised using response surface methodology [3], but very few have used the various programs that estimate drug concentrations and predict the effect of drug combinations, even fewer while in the operating theatre. Most anaesthetists do not even perceive a need for them. With evidence that anaesthetic drugs may cause long-term adverse effects, there is renewed interest in drug dosing.

New displays from GE Healthcare and Dräger try to translate the wealth of PK/PD research to create tools intended for everyday clinical practice. These displays show past and present estimates of IV drug concentrations and predicted effects of our combined anaesthetic drugs, as well as predicted future paths if one continues (or changes) drug dosing. Are the predictions accurate (or at least accurate enough)? Effective graphic displays of complex information have improved decision-making in high-risk environments. Early indications are that these displays are useful for teaching, but also clinically during induction, maintenance and recovery from anaesthesia [4]. More formal studies are required before we know whether these displays can promote more efficient or safer anaesthesia.

References

1. Fioratou E, Flin R, Glavin R, Patey R. Beyond monitoring: distributed situation awareness in anaesthesia. Br J Anaesth 2010 July;105:83-90.
2. Gin T. Clinical pharmacology on display. Anesth Analg 2010 Aug;111:256-8.
3. Short TG. Using response surfaces to expand the utility of MAC. Anesth Analg 2010 Aug;111:249-51.
4. Kennedy RR. Seeing the future of anesthesia drug dosing: Moving the art of anesthesia from impressionism to realism. Anesth Analg 2010 Aug;111:252-5.