Propofol-induced cardiovascular depression: science and art

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Editor—We have been following the correspondence by Drs Green, Kakazu and Lippmann, beginning with the publication by Möller Petrun and Kamenik reporting the relative effects of propofol and etomidate on cardiovascular parameters measured at the same depth of anaesthesia assessed by the bispectral index (BIS).

It is widely accepted that propofol causes more cardiovascular depression and hypotension than its forerunners, thiopentone and alfaxalone (Althesin), and its contemporary induction agent etomidate. Anaesthetists are well skilled in the art of minimising these potentially deleterious effects by using the manoeuvres employed by Möller Petrun and Kamenik: a fluid preload, co-administration of an opioid and a small ‘slow bolus’ of the induction agent over approximately 3 min.

Scientific understanding of the basic mechanisms underlying the decreases in blood pressure and cardiac output offer a chance to improve the art. We are taught that anaesthetic drugs cause cardiovascular effects by a number of mechanisms:

- CNS depression. This was controlled between treatments to some extent by Möller Petrun and Kamenik, although one must remember that the BIS reflects cerebral cortical function, not activity of the brainstem where cardiovascular tone is generated.
- Direct effects on the myocardium, impossible to measure accurately in intact humans or animals because a decrease in measurement values of an inotropic state, such as dP/dt max or the rate of shortening of ventricular muscle assessed by ultrasound techniques, are also affected by the amount of autonomic nerve stimulation, heart rate and the tone in the peripheral vasculature.
- Direct effects on the peripheral vasculature, veins and arteries that are also under the influence of sympathetic tone.

We faced these issues in 1989 when we performed two preclinical studies to investigate why propofol seemed to cause more hypotension than other agents. The results were applied clinically and described in the management of the propofol anaesthetic for surgical correction of hypertrophic obstructive cardiomyopathy. Elements of the cardiovascular system were studied in the absence of autonomic nervous system control and exposed to a range of propofol concentrations:

- an in vitro study of isolated veins and arteries and a study in anaesthetised dogs that had bilateral common carotid ligation, bilateral vagotomy, constant rate cardiac pacing and large doses of bretylium tosylate and propranolol. These showed clearly that normal plasma concentrations of propofol encountered in clinical anaesthesia did not cause a negative inotropic effect but caused relaxation of veins and increased capacitance with no direct effect on arteries and arterioles except at propofol concentrations above the clinical range.

Therefore the science would suggest that the way to manage the cardiovascular side effects of propofol anaesthesia is to manage the decrease in preload, either by giving fluid judiciously or simply by elevating the legs to improve venous return. The latter effectively transfers blood to the central capacitance compartment in a reversible manner. This is exactly what we reported in the case of hypertrophic obstructive cardiomyopathy managed with a propofol total intravenous anaesthesia technique. This manoeuvre led to a small increase in cardiac output during induction with no hypotension. Kakazu and Lippmann have misquoted us. We did not, nor have we ever advocated the use of phenylephrine as suggested by Bidd and colleagues. Indeed, we consider phenylephrine to be primarily an arteriolar vasoconstrictor. Since the science shows propofol to be a venodilator, the use of phenylephrine is illogical and, as Kakazu and Lippmann say, it may cause deleterious effects.

Science continues to search for an anaesthetic induction agent with a cleaner cardiovascular profile. Central to this search must be a comparison of agents based on the same depth of anaesthesia. In the past this has been achieved by using equivalent doses, such as the work by Sear and colleagues with the alfaxalone preparation Althesin and later by Monk and colleagues with propofol using exactly the same experimental paradigm in the same type of patient, administration of the ‘minimal infusion rate’, which is the smallest dose needed to block movements in response to a surgical incision of the skin in patients having peripheral vascular surgery. That approach showed alfaxalone caused minimal cardiovascular depression compared with propofol, which unfortunately replaced alfaxalone because of the anaaphyloctoid reactions to the CremophorEL excipient in Althesin. Propofol and alfaxalone were never compared in experiments using BIS as described by Möller Petrun and Kamenik until recently. A new water-soluble preparation of alfaxalone has been compared with propofol using BIS to compare the drugs at equivalent depths of anaesthesia. Again, propofol has been shown to cause significantly greater cardiovascular depression.

Balancing anaesthetic drugs and their side effects and the needs of patients continues to be an art guided by science. Science suggests that the cardiovascular depression caused by propofol can be ameliorated by appropriate management of preload.
The alternative is to use a different agent with fewer cardiovascular side effects. The only currently available agent is etomidate, as suggested by Möller Petrun and Kamenik. The new aqueous formulation of alphaxalone may fulfil this role in the future.

Declaration of interest
Colin Goodchild and Juliet Serrao are directors at Drawbridge Pharmaceuticals, the company developing a new aqueous formulation of alphaxalone called Phaxan.

References