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Editorial

The 'propofol infusion syndrome': myth or menace?

New diseases and syndromes are continually being discovered and described. Unfortunately, they do not come with identifying labels, but insinuate themselves into the clinical scene as widely dispersed, and frequently poorly substantiated case reports. The discovery of a novel, discrete clinical entity requires considerable clinical acumen paired with an acute sense of pattern recognition. The progression from first description to textbook knowledge can be exceedingly difficult if the events are rare; many now well-recognized pathological conditions, such as AIDS or Creutzfeldt–Jacob disease, were initially described as isolated occurrences of ill-defined symptom complexes before being identified as distinct disease entities with a specific cause.

Examples that come to mind in the context of anaesthesia are malignant hyperthermia and its relationship to trigger substances, 'hepatitis' subsequent to repeated halothane administrations or mortality due to etomidate sedation of intensive care patients. All of these conditions were initially described in individual case reports and the existence of an underlying cause was heatedly contested until the causal relationship was unequivocally demonstrated or the underlying pathophysiological mechanism was found.

The 'propofol infusion syndrome', currently the focus of a controversial discussion, is a case in point. Several authors have reported on intensive care patients dying under, as they saw it, unexplained circumstances with a distinct pattern of symptoms, in whom sedation with propofol was described as the one common factor [1,2]. Although they infer from their data that the substance was causally responsible for the detrimental and mostly fatal course, the available data is still insufficient to determine beyond reasonable doubt if this rarely occurring event actually is caused by the administration of propofol, and some authors contest the very existence of the syndrome [3]. But, although the available evidence does not confirm the connection, it is compelling enough to warrant a careful evaluation of all reported cases and a continuing high degree of clinical suspicion.

In 1992, Parke and colleagues reported five instances, in which critically ill children under propofol sedation developed metabolic acidosis and fatal myocardial failure [1]. Six years later, Bray reviewed 18 cases, including the original five, in which critically ill-children suffering from sepsis and/or severe respiratory disease and under sedation with propofol developed a variety of clinical symptoms with a high mortality rate [4]. Bray proposed that these were the manifestation of a clinical entity presenting with the following symptoms: metabolic acidosis, refractory cardiac failure, persistent bradycardia refractory to treatment, fever, lipaemia and evidence of muscle cell damage. He thought that this was causally linked to the propofol administration and gave the 'syndrome' its name.

Cremer and colleagues described the occurrence of a similar clinical picture in adult intensive care patients with head injuries or multiple trauma [5]. He proposed diagnostic criteria that differed from those in children and excluded patients with evidence of sepsis, multiorgan failure, and known causes of hyperkalaemia, acidosis or rhabdomyolysis.

Although the term 'propofol infusion syndrome' had been coined to emphasize the fact that propofol had been administered to these patients for a prolonged length of time and with increasing doses, no instance of this 'syndrome' has been reported in patients receiving propofol infusions in high doses for prolonged anaesthesia. In addition, the heterogeneity of the reported cases and the paucity of hard cardiovascular and metabolic monitoring data make it difficult to argue a single causal factor underlying every occurrence. The symptoms themselves are those commonly seen in varying combinations in critically ill and moribund patients, and can easily be attributed to other factors, such as impaired microcirculation,

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sympathetic neuropathy as part of critical illness neuropathy or septic cardiomyopathy, among others.

On the other hand, the evidence for the lethal effects of etomidate in critically ill patients was merely circumstantial and inferential at the beginning. Only after it was discovered that etomidate suppressed cortisol synthesis together with the observation that intensive care patients with low or falling plasma cortisol levels had a high mortality rate, did the proposed causal relationship gain clinical credibility. One can therefore not summarily dismiss the possibility that propofol, while innocuous when administered to the normal surgical patient, might precipitate a fatal course of events in patients with sepsis or systemic inflammatory response syndrome.

One common denominator in the patients who developed symptom complexes resembling the described 'syndrome', was the presence of impaired systemic microcirculation with tissue hypoperfusion and hypoxia – a common feature in patients with sepsis and systemic inflammatory response syndrome. The large number of patients with severe head injuries and cerebral oedema implicates the therapy modalities of fluid restriction and vasopressor infusions as relevant causative factors, since these ultimately cause a deterioration of tissue microcirculation.

According to the information provided by the manufacturer there was not a single documented patient with a symptom complex resembling the 'propofol infusion syndrome' in their controlled clinical trials on propofol sedation. However, as the adage correctly says, the absence of evidence is not evidence of absence, and one can only use the negative data of these studies to calculate a probable maximum occurrence rate. Assuming that 1000 patients participated in controlled clinical trials of propofol for sedation in intensive care patients and that there was, in fact, no incidence of the 'propofol infusion syndrome', the calculation shows that there is a 95% probability that the true incidence is one in 270 patients or lower. Although this seems high, it is still much lower than the incidence of 33% calculated by Bray from his data. In view of the rarity of reported events, the actual maximum incidence is likely to be very much lower.

AstraZeneca, the manufacturer of propofol, has the largest database of adverse event reports on the use of propofol. In a review of the literature in this issue of the *European Journal of Anaesthesiology* [6], representatives of the company analyse published reports and present hitherto unpublished data relevant to the interpretation of the available reports relating to the 'propofol infusion syndrome'. While they understandably approach the reports with some scepticism, they do not entirely discount the possibility of its existence and describe the changes that have been implemented in the prescribing information to reduce a possible risk by contraindicating the use of propofol for sedation in groups of patients possibly at risk of developing the syndrome.

A number of crucial questions remain to be resolved. The first of which is, of course, the question of whether propofol contributes to the occurrence of cardiovascular instability and metabolic derangement in intensive care patients. The available data actually does suggest that infusion rate and duration of administration could be relevant factors for the development of the 'syndrome', but whether this is not simply an epiphenomenon of the underlying pathology remains to be determined. If, however, propofol is implicated in the development of the symptom complex and there is a 'too much' and a 'too long' pertaining to administration, how can one define 'not too much' and 'not too long'? What are the consequences of the results of these studies for anaesthesia? This is not a question that can be tested in controlled studies, but must be decided, if necessary, on the basis of case reports.

It appears that the use of propofol for anaesthesia is not associated with the development of the symptom complex described in intensive care patients. Even in lengthy procedures, the propofol infusion does not last long enough to induce tolerance with grossly increased infusion rates, and the actually required dose is usually further reduced by the combination with an opioid. The dosage of propofol is thus well within the limits set by the manufacturer and any call for a restriction in its use for anaesthesia is unfounded.

The situation in intensive care is obviously much more complicated and the total doses of propofol much higher than those infused during anaesthesia. Children appear to be at greater risk of developing the symptom complex than adults, although the data are conflicting [2,7–9]. However, some paediatric hospitals and departments have gone to the extreme of banning the use of propofol completely, even for short-term sedation for diagnostic procedures or for anaesthesia. This is obviously an exaggerated response, since any alternative to propofol has its own well defined, and possibly even greater risk (e.g. volatile anaesthetics and hyperthermia). But what response would be rational and justified?

The uncertainty surrounding this phenomenon is great and has already provoked ill-considered reactions. There is now adequate data to allow a final statement on the safety of propofol in anaesthesia and to make cautionary recommendations for its use in intensive care sedation. This is a task that should be on the agenda of national and international societies in the near future. What is required are guidelines for adult and children aimed at regulating the administration of the drug to those it could possibly harm, and yet not withholding it from those who could benefit from its use.

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