International Journal of Obstetric Anesthesia (2013) 22, 175–178
0959-289X/$ - see front matter
http://dx.doi.org/10.1016/j.ijoa.2013.03.015

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EDITORIAL

Up-to-date or out-of-date: does thiopental have a future in obstetric general anaesthesia?

The unique nature of obstetric general anaesthesia (GA) places many demands on the properties of an induction agent. According to Chestnut's Obstetric Anesthesia, the primary goals of an induction agent for caesarean section (CS) under GA are; ''to preserve maternal blood pressure, cardiac output and uterine blood flow; minimise fetal and neonatal depression, and to ensure maternal hypnosis and amnesia''.[1] Furthermore, in many countries, it is the emergency CS for which GA is most frequently employed. At these times conditions may be adverse, time pressure extreme and these situational factors present other challenges. Can the induction agent be safely reconstituted in the time available or prepared in advance and stored safely for emergency use? Drug preparation and administration errors are more common in emergency situations,[2] and are these influenced by our choice of induction agent? Other considerations include: cost, familiarity, shelf life, effect on intubating conditions, whether licensed for use in pregnancy and impact on maternal recovery. Finally, and arguably most importantly, the overall value of any drug is considerably influenced by its availability and reliability of supply.

Many obstetric anaesthetists practicing in the UK will be familiar with a daily ritual that aims to mitigate some of the associated risks of emergency obstetric GA. Each day, an ampoule of thiopental is reconstituted and a syringe prepared, labelled, and placed in the drug fridge for use should an emergency present.[3,4] At the end of a day (or a variable amount of time), if not administered, the syringe of thiopental is discarded and the ritual repeats itself over again. In a 2007 UK survey, routine pre-preparation of emergency drugs was reported in 87% of obstetric units,[3] and although this practice may be on the decline, it still occurs in over half.[4] Whether pre-prepared or not, it is clear that, in the UK at least, the popularity of thiopental in obstetric GA has waned little. A recent survey of UK consultant obstetric anaesthetists by Murdoch et al. found thiopental was routinely used by 93% of respondents for induction of GA for CS.[5]

The enduring popularity of thiopental in the UK is no doubt a consequence of the substantial body of evidence that supports its safety and efficacy in obstetric GA, but use in other parts of the world is less. Although accurate information is limited, alternative agents are routinely used for CS under GA in many countries, including the USA, where thiopental was once considered the 'drug of choice'.[6,7] The shift away from thiopental has been a consequence of problems with drug supply, rather than of emerging clinical advantage of alternative drugs. UpToDate®, self-described as the 'premier evidence-based clinical decision support resource', concisely illustrates the current situation, by stating, in regard to obstetric GA that; ''a once-popular induction agent, thiopental, is no longer available in the United States.''[7] This succinct observation fails to convey the perceived importance of the drug to anaesthetists in the USA; discontinuation of the domestic production of thiopental in 2011 prompted the American Society of Anesthesiologists to urge the Food and Drug Administration to import thiopental from foreign manufacturing sites, stating that, ''in obstetric anesthesia, thiopental is still the drug of choice for induction of general anesthesia administered during cesarean delivery.''[6] Currently, thiopental remains available in the UK, but at the time of writing, its production by the sole UK manufacturer has temporarily ceased and UK supply is currently maintained by import from Germany on an unlicensed basis (personal communication, Archimedes Pharma Ltd., Reading, UK, March 2013). In light of the current situation affecting the UK and events elsewhere, perhaps now is an appropriate time to reappraise thiopental and its place in obstetric GA.

In the survey by Murdoch, more than a third of respondents cited historical reasons for their routine use of thiopental.[5] The time-tested routine of 'thio, sux, tube' has a long association with GA for patients considered at risk of pulmonary aspiration and a technique encompassing each of these three elements for obstetric practice was reported over 50 years ago.[8] Thiopental's long association with obstetric GA may, in some part, be a consequence of a lack of alternative induction agents with superior properties. Other drugs currently used for induction of GA for CS include; etomidate, ketamine and propofol, and the latter has generated debate as to its suitability for routine use at CS under GA.[9] Propofol entered clinical practice in the late 1980s, rapidly gained popularity, and comparative studies with thiopental for obstetric GA soon

followed.[10–16] Although these early studies produced conflicting findings, some uncertainty emerged regarding the safety of propofol with respect to both mother and baby.[9]

General anaesthesia for CS is associated with a higher incidence of intraoperative awareness than that reported in the general surgical population.[17] Awareness is distressing and a prominent cause of obstetric GA-related litigation in the UK.[18] A third of respondents in Murdoch's survey based thiopental choice on the increased risk of awareness with alternative induction agents.[5] These concerns may stem from a small study that found unacceptably high rates of awareness (40%) following propofol induction for elective CS.[19] However, aspects of the anaesthetic technique in this study may have contributed to this finding since halothane, administered at 0.25–0.5% with 50% nitrous oxide in oxygen for maintenance of anaesthesia, was discontinued between uterine incision and delivery. Other comparative studies of thiopental and propofol found no difference in rates of awareness, although these and other studies of women undergoing elective surgery were not adequately powered to identify a difference in this complication, nor were standardised methods of identifying awareness employed.[10,11,13,16] The lack of evidence of an increased risk of awareness with propofol and absence of accumulating clinical reports given the extensive worldwide use of propofol in obstetric anaesthesia, are no doubt reassuring.

The clinical safety profile of maternal propofol administration on neonatal outcomes is perhaps less clear, and data from a range of studies using different methodology are mixed.[9] Poorer Apgar scores were reported in neonates of women administered propofol for CS under GA compared to those with thiopental.[10,12] In one study, propofol induction was associated with inferior neonatal neurobehavioural measures, but these effects were short-lived.[12] In contrast, several comparative studies of propofol and thiopental have found no difference in neonatal outcomes.[11,14–16] Importantly, there are no large-scale studies in the setting of emergency obstetric GA in which the fetus may be distressed but its exposure to anaesthetic drugs brief. There is emerging interest in the influence of fetal exposure to anaesthetic agents on early brain development, and animal studies clearly show an adverse effect, especially when exposure occurs in the second trimester.[20] Human studies are limited, and there are no long-term neurodevelopment follow-up studies on infants exposed to maternally administered anaesthetic agents at CS. While there is no evidence that propofol for maternal induction conveys a clear advantage to the neonate over thiopental, evidence is lacking that propofol is more hazardous.

What about the effects of propofol on maternal haemodynamics? Clearly, the period from induction to delivery represents the key interval for investigation, since pre-delivery hypotension may adversely affect neonatal condition and blood pressure elevation at laryngoscopy and intubation may have maternal implications. Several studies have found that propofol obtunds the increase in maternal blood pressure at laryngoscopy and intubation compared to thiopental.[10,13–16] In one study, maximal maternal noradrenaline concentrations were found to be greater in women induced with thiopental, compared to propofol, however there was no difference in maternal adrenaline concentrations or neonatal outcome between groups.[15] The clinical significance of these observations remains unclear.

Despite the continuing popularity of thiopental for obstetric GA in the UK, other induction agents have largely replaced its use in emergency GA for non-obstetric patients considered at risk of pulmonary aspiration.[21] In a survey of Welsh anaesthetists, thiopental was used by 88% of respondents for emergency obstetric GA but less frequently than other induction agents for non-obstetric cases requiring rapid sequence induction and intubation.[21] Consequently, anaesthetists' experience with thiopental is declining and, in the context of obstetric emergency GA that is infrequent and largely unpredictable, using an unfamiliar induction agent at such times is not ideal. Encouraging thiopental use outside obstetric practice to improve familiarity is an approach supported by some,[5] but appropriate opportunities are likely to be infrequent.

Infrequent use of thiopental presents other problems. Drug administration errors, including 'syringe-swap' (a drug administered from a syringe whose contents were correctly labelled but the drug was not the one intended) are an important cause of anaesthesia-related morbidity and inattention, haste, distraction and fatigue have been associated with their occurrence.[2] These situational factors feature commonly at obstetric emergencies and it is no surprise that drug errors arise at these times.[17,22,23] The most common serious drug error reported in UK surveys of obstetric anaesthetic practice is administration of thiopental instead of antibiotic (or vice-versa).[4,24] The consequences, inadvertent GA or absence of intended GA with risk of awareness, are serious and potentially damaging. Although the true frequency of these events is unknown, their common reporting in surveys of drug errors in obstetric anaesthesia is concerning, and a recent UK patient safety report has highlighted this risk in obstetric practice.[22] In addition to 'syringe-swap' errors, some drugs are prone to reconstitution error. This has been reported at emergency CS; failure to reconstitute thiopental led to administration of water for injection followed by suxamethonium and consequent awareness.[17] Evidence-based strategies have been developed to reduce the risk of intravenous drug administration errors.[25] However, it is clear that certain drugs, including thiopental and antibiotics, are more commonly implicated in obstetric anaesthesia-related drug error incidents, partly because of the frequency