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Editorial

Tramadol – the Marmite™ drug

In this issue of *Anaesthesia*, Stevens et al. [1] provide more evidence for the complexity of tramadol usage. Tramadol was only licensed in the UK 30 years ago, yet in its short lifetime it has attracted a disproportionate amount of attention. From being relatively unknown outside the realms of anaesthesia and pain management, it now not only divides opinion within our specialty but has generated a real public awareness; it was held partly responsible for a number of collisions that occurred during professional cycling races in 2014 [2] and features in the title of controversial comedian Frankie Boyle's Channel 4 series *Tramadol Nights* [3]. It is therefore timely that we re-evaluate its use in anaesthesia, analgesia and peri-operative medicine.

Pharmacology of tramadol

Tramadol hydrochloride is a synthetic analgesic that acts as a non-selective μ-, κ- and δ-opioid receptor agonist, blocking ascending pain signals as well as altering the cortical perception of pain by inhibiting the re-uptake of serotonin and noradrenaline. This re-uptake inhibition may also play a role in modulating descending pain pathways in the spinal cord [4]. Although classified as an opioid, only about 30% of tramadol's activity can be reversed with naloxone [4], and it is these non-opioid actions that set tramadol apart from other drugs. Minimal respiratory depression

allow its use as an adjunct with patient controlled analgesia (PCA) systems and in the pre-hospital setting [5]. The lack of effect on the respiratory centre has also made tramadol by default, the 'weak opioid' of choice in paediatrics following the withdrawal of codeine [6]. However, it is also the serotoninergic and noradrenergic effects that give tramadol its most troublesome reported side-effects: sedation [7]; lowering of the convulsion threshold [8]; and delirium [9].

Tramadol is a racemic mixture of two enantiomers: (+)-tramadol and (−)-tramadol. Unlike other racemic drugs such as bupivacaine, ketamine and ibuprofen, these enantiomers are complementary: (+)-tramadol has a much greater effect on serotonin, reducing re-uptake and activating its release; whereas (−)-tramadol has a much greater potency for inhibiting noradrenaline re-uptake and activating α-adrenergic receptors [10]. The effect of tramadol on μ-opioid receptors is almost entirely due to an active metabolite, O-desmethyltramadol, which is a significantly more potent opioid than the parent drug, with additional noradrenaline re-uptake inhibiting properties. This is important because it has 200 times the μ-affinity of (+)-tramadol (thus increasing the likelihood of nausea and vomiting) and is longer acting, having an elimination half-life of nine hours compared with six hours for tramadol itself [11]. Tramadol is a substrate for the cytochrome P450 CYP2D6 liver enzyme, hence any agents with the ability to inhibit or induce this enzyme will probably interact with tramadol. There are many different alleles coding for activity of the CYP2D6 enzyme system, as well as gene duplication in a number of ethnic groups. This results in a wide spectrum of enzyme activity (phenotype) across the range of different genotypes, called genetic polymorphism. At one end of the spectrum, two abnormal genes lead to individuals with no CYP2D6 enzyme activity, so-called poor metabolisers. At the other extreme, duplication of alleles results in individuals with unusually high CYP2D6 enzyme activity (ultra-rapid metabolisers). Ultra-rapid metabolisers are particularly prevalent in Ethiopia (29%) and Saudi Arabia (21%) and are thought to be an evolutionary development in relation to diet [12].

A typical Caucasian population in the UK consists of 5-10% poor metabolisers and 0.03% ultra-fast metabolisers [13]. As with codeine, in the 5-10% of the population that have reduced CYP2D6 activity (hence reduced levels of O-desmethyltramadol), there is a reduced analgesic effect and patients require a dose increase of 30% in order to achieve the same degree of pain relief as in those with a normal level of CYP2D6 activity. Indeed, over 50% of ethnic Chinese have reduced CYP2D6 activity with a consequent reduction in tramadol efficacy [14]. Pharmacogenetic testing (the AmpliChip CYP450 Test) [15] is a promising tool to customise tramadol treatment, but the costs associated with testing (£365-790; $600-1300; €437-946) do not justify its routine use in clinical practice at the moment, even though this has been suggested.

Drug interactions

Tramadol has multiple interactions with other drugs, due in part to its multi-system mechanism of action and also because of its reliance on the aforementioned CYP2D6 system for metabolism. The selective serotonin re-uptake inhibitors (SSRIs) are the main group of drugs that interact with tramadol. This is primarily because they act to increase serotonin and are some of the most potent inhibitors of CYP2D6, thus leading to a real risk of serotonin syndrome when used together [16]. This is also a problem if tramadol is co-administered with monoamine oxidase inhibitors and some atypical antipsychotics [17]. Tramadol interacts with ondansetron, owing to their opposing effects on the serotonergic system. There is also potential for a pharmacokinetic interaction because ondansetron is partly metabolised by the CYP2D6 enzyme system. The combination of all these factors results in a reduced potency of both when the the two drugs are used together [1].

Evidence for use

Robust evidence for the benefit of tramadol is lacking. Many studies are small and the pooled data are heterogeneous. This is not unique to tramadol but common to many analgesics, particularly in the peri-operative period. This is partly because there is no universal outcome for all analgesic trials [18, 19] and partly because the pain relieving effect of many drugs in the peri-operative period is assessed in terms of their morphine-sparing effect; however, this does not mean they have any analgesic activity

when used alone, as is the case with magnesium, for example [20].

There is virtually no evidence for tramadol's efficacy in treating acute postoperative pain, despite its widespread prescription. In addition, although it appears in guidelines for the management of chronic pain [21], the level of evidence is often poor and side-effects may outweigh benefits for individual patients. Where tramadol has been proven to be useful is in chronic neuropathic pain, with a Cochrane-generated meta-analysis demonstrating efficacy [22]. There is also enough pooled evidence to recommend tramadol in the prevention of premature ejaculation [23], where its mechanism of action is related to enhanced serotonin levels; however, its use in this context is beyond the scope of this editorial.

Misuse of tramadol

Much of the popularity of tramadol relates to the fact that it was one of the few 'opioids' that was not controlled under the Misuse of Drugs Act (1971). However, in 2013 the UK Advisory Council on the Misuse of Drugs recommended that tramadol be re-classified as a Class C drug [24], and the US Food and Drug Administration followed suit in 2014. Legislation surrounding the legal use of tramadol has therefore been strengthened – it was placed in Schedule 3 of the Misuse of Drugs Regulations 2001, but without application of so-called 'safe custody requirements' (i.e. it does not need to be kept in a locked controlled drugs cabinet). Although the UK Government was keen to implement Schedule 3 in full, concerns were raised by doctors, pharmacists and prison governors that this would significantly impact on the care of those in prisons, custody suites and youth offender institutions [25]. Thus, it may still be stored on the open shelf in pharmacies.

Regulatory changes also affected import and export rules; previously, tramadol was freely available to buy on the internet, where patients could obtain it in bulk from foreign countries, and this may have been responsible for the rapid increase in tramadol-implicated deaths (there were two deaths in the UK in 1998 and 154 in 2011 [26]). Many of these deaths were not thought to be due to tramadol alone, but to its interactions with other drugs. However, there has also been a increase in the legitimate prescribing of tramadol – the number of prescriptions nearly doubled from January 2006 to December 2012 [27]. The reasons for this increase are not clear; there have been no 'landmark' studies that have driven it. More importantly, perhaps, has been the ability to prescribe tramadol in the community without the regulatory paperwork that exists with controlled drugs; many of us would like to think that we always make decisions based on clinical need, but we almost always default to the 'easier' option [28]. It will be interesting to see if the rise in tramadol prescriptions continues after the change in legislation.

So who abuses tramadol? The most publicised are professional sportsmen such as rugby players and cyclists because it is only 'monitored', but not banned, by the World Anti-Doping Agency (WADA). It is taken in the professional peloton to alleviate the aches and pains of cycling hundreds of miles each week. In 2014, its use was linked to a large number of crashes occurring towards the end of one-day 'Classics' races, where it was implied that impaired judgement due to tramadol may have been responsible when groups of riders were close together at speed, jostling for position [2]. Team Sky, along with a number of other professional cycling teams, have distanced themselves from its use, believing that administration during racing and in training is unethical [29].

There is, however, little evidence to suggest high levels of dependence in the general population. It is certainly less addictive than morphine and codeine, and the total number of people with dependence probably amounts to around 200 in the UK [27], although the numbers are thought to be rising. The data surrounding overall recreational use is much less reliable and vague, but most areas of the UK are reporting an increase in use [30] and O-desmethyltramadol is now due to be scheduled as it was being sold as a 'legal high' [31].

Tramadol in children

Following the tragic deaths of several children after the administration of codeine [32] and a subsequent warning notice issued by the Medicines and Healthcare products Regulatory Agency [33], a joint statement by the Royal College of Anaesthetists (RCoA), the Association of Paediatric Anaesthetists (APA) and the Royal College of Paediatrics and Child Health

(RCPCH) was released in November 2013 [34] related to the use of codeine in children. Their conclusions were non-committal; "*Within the UK different solutions are being employed. These include continuing to use codeine with increased caution or adopting alternative opioid medication regimens: oral morphine, dihydrocodeine, oxycodone or tramadol are potential alternatives.*" An editorial was subsequently published in this journal discussing the place of codeine in mothers and children [35] and there has since been an increase in the number of tramadol prescriptions issued, although it is not licensed for use in children under 12 years old.

As in adults, the evidence base for the effectiveness of tramadol in children is weak, with many studies including relatively small numbers of patients. The majority of trials in children have been performed in patients undergoing adenotonsillectomy. It has been administered intravenously, where it is more effective than placebo [36]. It was equally efficacious to a single intraoperative dose of morphine in one small study [37], but in another trial morphine was superior [38], as is to be expected. It has also been administered topically to the tonsillar bed [39] and by local infiltration [40, 41]. In both of these trials it was equivalent to ketamine in terms of efficacy. In one study, sublingual tramadol (2 $mg.kg^{-1}$) vs sublingual ketorolac (0.5 $mg.kg^{-1}$) vs control resulted in similar analgesia for both treatment groups in children with suspected bone fracture or dislocation managed in the emergency department [42].

Is tramadol safe?

With the rise in the number of prescriptions for tramadol in both adults and children there has been an associated increase in the number of reports related to accidental or deliberate overdose. Morley et al. [43] found one tramadol-related paediatric death out of ten toxicologically-related deaths over a six-year period in one UK hospital. Li et al. [44] reported two children who suffered convulsions caused by continuous intravenous infusions of tramadol, whilst Grandvuillemin et al. [45] reported two children with severe hypoglycaemia also thought to be related to tramadol. Marechal et al. [46] described the case of an eight-month-old child who developed extreme agitation, fever and tachycardia (serotonin syndrome) after accidental ingestion of a single 200-mg tramadol tablet, and Perdreau et al. [47] reported cardiogenic shock in a seven-year-old. Intoxication was confirmed by the finding of high serum levels of both tramadol and O-desmethyltramadol. Fortunately, the patient made a full recovery. The analgesic effects of tramadol are only partially reversed by naloxone (and its administration may actually result in an increased risk of convulsions), but also by α_2-adrenergic receptor antagonists such as yohimbine [48] and also ondansetron [1].

Conclusion

Until there is a substantial body of evidence of either benefit or harm, doctors will continue to prescribe tramadol based on personal preference rather than clinical evidence. Mechanistically, tramadol does have some appealing properties, despite its interactions and adverse effects, that may make its continued presence in armoury of the anaesthetist worthwhile, for the moment at least.

Marmite™ has been produced for over 100 years, and still remains a staple of most kitchen cupboards in the UK [49]. We hope that over the next 70 years we may discover whether we really love or hate tramadol.

Competing interests

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Editorial

Awareness in cardiothoracic anaesthetic practice – where now after NAP5?

Cardiac anaesthesia has historically been associated with a higher incidence of unintended awareness compared with other anaesthetic subspecialties [1, 2], but the incidence in modern practice is less certain. The incidence in thoracic anaesthesia is also unclear, mainly because so few studies have addressed this issue at all [3, 4]. The recent publication of the 5th National Audit Project (NAP5) report [5] now provides cardiothoracic anaesthetists with a useful point for reflection on current practice.

The reported incidence of unintended awareness in cardiac practice ranges from less than 1% to over 20%, depending on the definition of awareness, the size of the study and the method of detection (Table 1). The early studies [6–8] included fewer than 60 patients each, so were subject to sampling error, and were carried out during the era of high-dose opioid anaesthesia. The later studies were prospective, used a balanced anaesthesia technique, and included 600-900 patients, finding an incidence of 0.3-1.14% [11–13]. The incidence in the cardiac cohort of a large US multicentre study was similar, at 0.44% [2]. Cardiac anaesthesia was thus associated with a two- to tenfold higher risk of unintended awareness than that reported for the general population [2, 16].

The more recent B-Aware [3], B-Unaware [14] and BAG-RECALL [15] studies specifically recruited patients considered to be at high risk of awareness, so a third to a half of these cohorts were cardiac patients. However, they were not specifically cardiac studies, leading to a relatively small cardiac cohort in B-Unaware (525/1941 patients overall). The incidence of unintended awareness in cardiac patients in these studies varied from

