European Journal of Anaesthesiology 2000, **17**, 657–661

EDITORIAL

Opioid detoxification under anaesthesia

Introduction

Opioid dependence and addiction is a complex psychosocial problem with far-reaching consequences for the individual, their family and acquaintances and for society. Opioid addiction, particularly to heroin, is associated with a high risk of medical complications – bacterial endocarditis, hepatitis, HIV infection and tuberculosis. There is a high death rate, 10–44 per 1000 per year among untreated addicts in the USA, much lower for those on a supervised methadone maintenance programme [1,2]. The term addiction is derived from the Latin addictus. In Roman law an addictus was a debtor surrendered to his creditor as a servant. Unlike a slave, the addictus could be released from his bondage when the debt was paid. Many drug addicts also want to pay their debt and be relieved of their bondage to the drug habit.

Treatment of opioid addiction

The traditional treatment of opioid addiction involves substitution of heroin by an equivalent-dose of a longer-acting opioid agonist, such as methadone, followed by gradual tapering of the methadone dose. Substitution therapy does not reverse opioid dependence, but when combined with rehabilitation support it can result in marked improvement in general health, psychological and social functioning, and a reduction in illicit drug use, criminal activity and risk of contracting HIV and other infectious diseases [3]. However, substitution therapy alone has a high initial dropout (30–90%) and early relapse rate [3,4], but may be a useful prelude to detoxification, i.e. removal of the opioid from the body, and subsequent abstinence. Detoxification programmes provide supervised withdrawal from a drug of dependence so that the severity of the withdrawal symptoms and serious medical complications are reduced to a minimum.

Rapid detoxification involves abrupt discontinuation of the opioid or administration of an opioid antagonist, such as naloxone or naltrexone, followed by maintenance therapy with oral naltrexone to discourage relapse. Withdrawing the opioid or antagonizing its action elicits various pathophysiological disturbances, collectively known as a 'withdrawal syndrome'. Withdrawal symptoms may be extremely unpleasant and appear some hours after withdrawal, peak by 48–72 h and largely disappear within 7–10 days. They are characterized by restlessness and an intense craving for the drug, accompanied by yawning, running nose, lacrimation, perspiration, aches and pains, dilated pupils, pilomotor stimulation and hypertension. Marked sympathetic activity accounts for most of these symptoms. There are profound increases in plasma catecholamines accompanied by cardiovascular stimulation [5–7]. The locus ceruleus (LC), the major noradrenergic nucleus in the brain, plays an important role in opioid dependence [8]. During opioid withdrawal neuronal activity in the LC is greatly increased, resulting in the noradrenergic surge responsible for many of the withdrawal symptoms [5]. Clonidine is widely used to suppress this noradrenergic hyperactivity, and is effective in relieving the withdrawal symptoms [9–11]. Unlike alcohol withdrawal symptoms, those associated with opioid withdrawal are very rarely life-threatening [12], but they are sufficiently aversive to act as a major deterrent to addicts who want to cease the habit.

Acute opioid detoxification under anaesthesia

A variant of rapid detoxification is where the addict undergoes the acute antagonist-precipitated withdrawal under anaesthesia. This method, sometimes referred to as ultra-rapid opioid detoxification, was introduced by Loimer and colleagues from Vienna in an attempt to minimize the psychological trauma associated with rapid opioid detoxification [13,14]. Detoxification under general anaesthesia has since become popular in several countries. A variety of anaesthetic techniques are used, the most popular

https://doi.org/10.1046/j.1365-2346.2000.00769.x Published online by Cambridge University Press

being total intravenous anaesthesia with propofol. The trachea of the patient is intubated to avoid aspiration. In most centres the lungs of the patient are mechanically ventilated, although some anaesthetists allow patients to breathe spontaneously. However, this may be less advisable because anaesthesia may last several hours. Further, respiratory rate and minute ventilation have been reported to increase by 80% to 100% during ultra-rapid detoxification [15]. EEG monitoring may be used to monitor anaesthetic depth and the effectiveness of detoxification [16]. The bispectral index (BIS) is widely used, although the median EEG frequency may be a more sensitive indicator of sympathetic activation and opioid reversal by the antagonist than the BIS [7]. A urinary bladder catheter and nasogastric tube should be inserted as standard. The introduction of octreotide, a somatostatin analogue, has been a major advance in controlling gastrointestinal hyper-secretion, particularly diarrhoea, which can otherwise be extremely profuse [17]. Clonidine should be given to attenuate the sympathetic and haemodynamic responses following administration of the opioid antagonist. When a stable level of anaesthesia has been established, an opioid antagonist is administered – oral naltrexone via the nasogastric tube is commonly used, but continuous intravenous infusions of naloxone or nalmefene are used in some centres [18,19]. Challenge doses of naloxone may subsequently be given to assess whether blockade of opioid receptors is complete. When no haemodynamic or EEG responses to naloxone occur, anaesthesia is stopped. An antiemetic should be given before the end of anaesthesia to minimize later emetic effects of the detoxification process.

Detoxification and the cellular basis for opioid dependence

The pharmacological basis for rapid detoxification remains unclear, but obviously it is intimately related to the processes associated with drug dependence [20,21]. As dependence develops, adaptive changes occur at the cellular level that compensate for the continued inhibitory effects of the opioid. Now the presence of the drug is required for normal functioning. Dependence is associated with alterations in several components of the cAMP signal transduction cascade. The transcription factor cAMP response element binding protein (CREB) is altered in response to several drugs of abuse, including opioids [22,23]. CREB is the major nuclear transcription factor responsible for elevated levels of cAMP and symptoms of withdrawal are significantly attenuated in CREB-knockout mice [24]. Chronic receptor stimulation causes compensatory, slowly developing increases in adenyl cyclase activity and elevations in cellular cAMP. This in turn induces cAMP phosphodiesterase and an increase in the rate of degradation of cAMP resulting in a negative feedback mechanism maintaining homeostasis of cAMP concentrations. The overshoot produced by antagonists is thought to be a result of this compensatory response suddenly occurring in the absence of opioid inhibitory effects [25]. Chronic exposure to opioids also may be associated with the appearance of constitutively active μ-receptors that do not require an agonist for signal transduction, and which counterbalance the upregulation of cAMP [26]. It is obvious that the cellular changes associated with long-term opioid exposure and dependence will take some time to recover and for homeostasis to be restored. The postwithdrawal phase is usually protracted and it may be several months before subjects are symptom-free [27]. Propofol anaesthesia may be associated with a shortened period of long-term withdrawal symptoms after detoxification [28]. During this secondary phase intensive psychosocial support is needed to prevent relapse.

Controversy surrounding detoxification under anaesthesia

Ultra-rapid detoxification under anaesthesia has generated considerable controversy, in particular with respect to its long-term effectiveness, a supposedly unacceptable high risk:benefit ratio, high costs and the safety of anaesthesia in these patients. There has been concern, particularly in the USA, about the proliferation of anaesthesia-assisted programmes at costs ranging from $2500 to $7500 or more, and the obvious risk of exploitation of vulnerable individuals [29]. Clinics often tout for patients by advertising in newspapers and on the Internet.

O'Connor and Kosten [30] have reviewed the literature on rapid and ultra-rapid opioid detoxification

https://doi.org/10.1046/j.1365-2346.2000.00769.x Published online by Cambridge University Press

techniques. They highlighted the shortcomings of many of the published studies – small number of patients, differences in protocols, lack of randomization and adequate control groups. Often only short-term follow-up outcomes were reported. In one study, outcome data were based only on a telephone survey [31]. More recent studies have attempted to address some of these criticisms. Hensel and Kox [32] reported that 49 of 72 patients (68%) were abstinent 1 year after detoxification under propofol anaesthesia. Albanese and his colleagues [33] reported a 65% relapse rate after 6 months. Although to date no controlled study has been published, a large, multicentre controlled study is currently in progress in the Netherlands (De Jong CAJ, personal communication).

Concerns about the ethics and safety of carrying out the process of detoxification under general anaesthesia have been expressed (by nonanaesthetists) [29,30]. Many of the arguments used against the use of anaesthesia have, however, been based on either out of date or inappropriate morbidity and mortality data [34]. Although there is always a risk, albeit small, associated with general anaesthesia, this can be considered justified as it is considerably less than the morbidity and mortality associated with continued opioid abuse [35]. Opioid addiction should be considered as a chronic medical condition [36]. General anaesthesia is commonly provided for patients with other medical conditions undergoing procedures simply because these would be extremely unpleasant without anaesthesia. So why not anaesthesia for acute detoxification? A proviso must be, however, that the anaesthesia is carried out by qualified anaesthesiologists and that the patients are cared for after the procedure in a properly staffed and equipped recovery unit. At least one postanaesthesia death has been reported, a patient found dead in bed 41 h after the procedure [19]. The cause of death was not reported. ECG dysrhythmias associated with prolongation of the QT interval have been reported after detoxification under anaesthesia and it was recommended that patients be regularly monitored for three days after the procedure [37]. Opioid overdose is a particularly serious hazard when individuals relapse to opioid use after detoxification because they are likely to revert to their previous dose of heroin or methadone. In the new circumstances, in which opioid tolerance is absent or much reduced, this can cause severe respiratory depression and this has been the cause of several deaths [38]. The situation will be exacerbated by naltrexone treatment, because chronic use of opioid antagonists results in receptor upregulation, with an increased sensitivity to agonist drugs [39–43]. It is crucial that addicts are made very aware of the risks involved in restarting opioid abuse, and warned that, if they do return to the habit, they should make appropriate adjustments in the doses of opioids they administer to themselves.

In conclusion, ultra-rapid opioid detoxification under general anaesthesia presents yet another challenge to the anaesthesiologist. Much research is still needed to determine whether this method results in better long-term benefits compared with more conventional methods. Nonetheless, it does appear to offer benefits, at least in terms of patient acceptance. If this allows more addicts to consider kicking the habit of opioid dependence then, in my view, it is worthwhile. Of course, detoxification is not a cure, but is only the first step in what, for many addicts, will be a long road to complete rehabilitation. Considerable psychiatric and social support is required in the months after detoxification if they are to achieve the goal of total abstinence.

J. G. Bovill

Professor of Anaesthesiology
Department of Anaesthesiology
Leiden University Medical Centre
PO Box 9600
2300 RC Leiden
The Netherlands

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