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Benzodiazepine dependence and its treatment with low dose flumazenil

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Globally benzodiazepines remain one of the most prescribed medication groups, especially in the primary care setting. With such high levels of prescribing it is not surprising that benzodiazepine dependence is common, cutting across all socioeconomic levels. Despite recognition of the potential for the development of iatrogenic dependence and the lack of any effective treatment, benzodiazepines continue to be widely prescribed in general practice. Conventional dependence management, benzodiazepine tapering, is commonly a protracted process over several weeks or months. It is often associated with significant withdrawal symptoms and craving leading to patient drop out and return to use. Accordingly, there is a worldwide need to find effective pharmacotherapeutic interventions for benzodiazepine dependence. One drug of increasing interest is the $GABA_A$ benzodiazepine receptor antagonist/partial agonist, flumazenil. Multiple bolus intravenous infusions of low dose flumazenil used either with or without benzodiazepine tapering can reduce withdrawal sequelae, and/or longer term symptoms in the months following withdrawal. Preliminary data suggest that continuous intravenous or subcutaneous flumazenil infusion for 4 days significantly reduces acute benzodiazepine withdrawal sequelae. The subcutaneous infusion was shown to be tissue compatible so the development of a longer acting (i.e. several weeks) depot flumazenil formulation has been explored. This could be capable of managing both acute and longer term benzodiazepine withdrawal sequelae. Preliminary *in vitro* water bath and *in vivo* biocompatibility data in sheep show that such an implant is feasible and so is likely to be used in clinical trials in the near future.

Introduction

In 1959 the clinical introduction of the first benzodiazepine, chlordiazepoxide (Librium), promoted as a safe tranquillizer heralded a new era in the 'control of personal and emotional problems' and was a landmark of modern psychopharmacology. In the space of a few short years and accompanied by sophisticated promotional campaigns many other benzodiazepines were developed and released, with diazepam (Valium) the best known, being marketed in 1963. By the 1970s and early 1980s benzodiazepines had become the most commonly prescribed class of drug in the world. Soon after their introduction, however, reports of benzodiazepine dependency emerged [1]. Initial reports of dependency were subsequently supported by studies in animals [2] and humans [3, 4]. Despite concerns about possible long term adverse effects of benzodiazepine use, and calls for research into these effects stemming from as early as 1980 [5], benzodiazepines remain one of the most widely prescribed class of drugs in the world. While many countries now have guidelines recommending short term use with minimum doses, these are frequently ignored with long term prescribing of benzodiazepines actually rising in certain socioeconomic groups, notably the elderly and those on concessionary benefits [5].

Benzodiazepine mode of action

Benzodiazepines enhance the effects of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the

central nervous system via a modulatory site on the $GABA_A$ receptor complex. $GABA_A$ receptors are a family of ligand-gated chloride channel inhibitory receptors and one of the main transmembrane neurotransmitter receptors in the brain. Each receptor consists of heteromeric subunits that form a pentamer of two α subunits, two β subunits and one γ subunit that in turn consist of a number of different subtypes. This underpins the binding of substances such as benzodiazepines, alcohol, barbiturates and neurosteroids, which differently affect $GABA_A$ function. For example, benzodiazepines increase the frequency of GABA-gated chloride ion opening in the presence of GABA, whereas high dose barbiturates can open this channel in the absence of GABA [6]– and thus barbiturates are especially dangerous at high doses. The benzodiazepines allosterically enhance the inhibitory actions of GABA by binding to the modulatory site located between the α_1, α_2, α_3 or α_5 and γ subunits. The α subunit subtype of the $GABA_A$ receptor is associated with the benzodiazepine clinical effect. The α_1 subunit (present in over 50% of all $GABA_A$ receptors) mediates the sedative and amnestic actions of benzodiazepines, the α_2 and α_3 subunits (present in 10–20% of all $GABA_A$ receptors) mediate the anxiolytic action of benzodiazepines [7] and the α_5 subunit appears to mediate memory/learning impairment activity [8]. The picture is further complicated by evidence that $GABA_A$ receptor mediated benzodiazepine effects may vary according to regional differences in expression of the receptors in the brain, variations in distribution of $GABA_A$ receptors on individual neuronal soma and dendrites, and synaptic *vs*. extrasynaptic locus [9].

Understandably, there is a great deal of interest in developing $GABA_A$ receptor subtype selective medicines to capture the desired clinical effect (e.g. discrete hypnosis, anxiolysis, or cognitive enhancement) without the side effects seen with current agents. The development of drugs with different binding affinities for α subunits has proven difficult, however, because the benzodiazepine binding site is highly conserved between α subunits. The development of drugs with selective efficacy for different α subunits is a promising alternative as these drugs bind with equal affinity to all α subunits, but selectively modulate the activity of one or some of them [10].

Our increasing understanding of the GABA receptor system has prompted attempts at revision of GABA nomenclature. The early pharmacological classification of BZ-I and BZ-II groups corresponds with modern molecular findings of $GABA_A$ subunit differences (e.g. α_1 in BZ-I, α_2, α_3, or α_5 in BZ-II) [11]. As benzodiazepines lack intrinsic activity at the $GABA_A$ receptor in the absence of GABA, the old terminology of agonists (e.g. diazepam), antagonists (e.g. flumazenil) and inverse agonists (e.g. FG 7142) is sometimes replaced by the terms positive allosteric modulators, neutral allosteric modulators and negative allosteric modulators, respectively [12]. Subtype-selective indirect modulators such as benzodiazepines could be called subtype-selective $GABA_A$ modulators (S-GAMs) with the appropriate specification of the subtype (e.g. zolpidem would thus be a $GABA_A$-α_1-S-GAM) [13]. As $GABA_A$ receptors are found synaptically as well as extrasynaptically, another approach proposed is to use the location of the receptor in the descriptor. Thus, drugs such as gaboxadol would be selective extrasynaptic $GABA_A$ agonists (SEGAs) and selective intrasynaptic agonists would be SIGAs, with the appropriate suffix for subunit composition [13]. No universally accepted classification system has emerged, although there is considerable need.

Theories of development of tolerance

Our current understanding of the mechanism of benzodiazepine tolerance is incomplete, hindered by a limited understanding of the mode of action of benzodiazepines, and difficulty reconciling clinical/preclinical and *in vivo*/*in vitro* data that is somewhat inconsistent. Benzodiazepine tolerance is believed to be an adaptive mechanism following chronic treatment, with tolerance to specific benzodiazepine effects occurring at differing rates and degrees. Sedative and hypnotic tolerance develops quickly (days), followed by anticonvulsant tolerance (months), whereas there is little evidence to support the anxiolytic tolerance developing at any time. There are very scarce data reporting on $GABA_A$ receptor subtype tolerance. However early preclinical data suggest that α_2/α_3 subtype selective compounds neither lead to tolerance nor withdrawal symptoms [9].

The few major reviews of this area [9, 14–16] postulate a number of theories of development of tolerance. $GABA_A$ receptor uncoupling (in which benzodiazepines exhibit a decreased ability to facilitate GABA-induced ion flux) has long been proposed, although the molecular mechanisms to affect this are poorly understood. Modifications in $GABA_A$ subunit expression as a mechanism of tolerance has obvious theoretical appeal. Unfortunately (preclinical) evidence to date is conflicting [17] and has been unable to validate this theory. Glutamatergic and GABA neuroanatomical interplay suggests a possible role of glutamatergic sensitization in benzodiazepine tolerance and withdrawal. There are some data to suggest that this system may at best be partially involved [9]. There exists evidence in support of monoamine and neurosteroid roles in benzodiazepine tolerance that is in the early stages of development. In brief, benzodiazepine tolerance is clearly a complex process that may well be mediated by multiple, overlapping mechanisms. Regional variation in benzodiazepine receptor subtype distribution, and challenges in translating from preclinical to clinical environments further confound our understanding of this important area.

Benzodiazepine dependence and withdrawal

Benzodiazepine use for as little as 3 to 6 weeks, even while adhering to therapeutic doses, is associated with the development of physical dependence, with between 15–44% of chronic benzodiazepine users experiencing protracted moderate to severe withdrawal symptoms upon cessation including emergent anxiety and depressive symptoms [2, 18, 19]. For longer term use approximately 40% of people on benzodiazepines for more than 6 months will have a moderate to severe withdrawal, and the remaining 60% will have a relatively mild withdrawal syndrome, if the drug is stopped suddenly. The development of dependence appears to be similar to that of other classes of addictive drugs, with benzodiazepines resulting in dopamine surges in the ventral tegmental area, and subsequent changes in glutametergic receptor expression, due to disinhibition of dopaminergic neurons [20].

Withdrawal symptoms can largely be divided into three main groups: anxiety and anxiety-related symptoms, perceptual distortions and major events (see Table 1). The cause of withdrawal is largely unknown, although there is some evidence for down-regulation of benzodiazepine binding sites in the $GABA_A$ complex, and for increased calcium flux and serotonin (5-HT) activity during withdrawal. Supporting evidence includes the finding that the calcium channel antagonist verapamil [21–23], the $GABA_B$ agonist baclofen [21, 24] and the $5\text{-}HT_3$ receptor antagonist zacopride [24], have all prevented withdrawal responses in rats.

A number of authors have described both an acute and a protracted withdrawal phase [25–27] with acute withdrawal lasting 5–28 days and protracted withdrawal lasting for up to 12 months or longer [27]. It has been estimated that between 10–25% of chronic benzodiazepine users suffer protracted withdrawal symptoms upon cessation [26]. Both psychological and physical withdrawal symptoms are common in both acute and protracted withdrawal and have been well described in the literature [5, 26, 28]. Severity of acute withdrawal has been shown to be associated with higher dosage of benzodiazepines, the use of multiple benzodiazepines, oral rather than injected use [29], duration of use, shorter half-life benzodiazepines and more rapid tapering [30]. Patient variables have also been indicated such as higher pretreatment anxiety and depression, personality pathology, panic disorder diagnosis, and history of alcohol/drug abuse [27]. These factors may also be predictive of longer term outcomes. For example high baseline levels of psychological distress, anxiety and dosage predict poor outcomes at 3 months following a supported outpatient dose taper treatment intervention [31].

After prolonged prescribing, benzodiazepines tend to lose their efficacy (i.e. tolerance develops) particularly for the sedative and anticonvulsant actions of benzodiazepines, although why this occurs is not completely understood [9].

Table 1

Symptoms and signs of benzodiazepine withdrawal

Anxiety and anxiety-related symptoms
Anxiety, panic attacks, hyperventilation, tremor, sleep disturbance, muscle spasms, anorexia, weight loss, visual disturbance, sweating, dysphoria
Perceptual distortions
Hypersensitivity to stimuli, for example hyperacusis; abnormal bodily sensations; depersonalization/derealization.
Major events
Seizures (grand mal type); precipitation of psychosis (e.g. hallucinations, delusions, and delirium)

Benzodiazepine withdrawal management

The absence or presence of withdrawal symptoms should be assessed (see Table 1). Conventional benzodiazepine withdrawal management in primary care commonly involves gradual reduction in benzodiazepine dose, also known as 'benzodiazepine taper' with switching to a longer half-life benzodiazepine or adjunctive medications having a more limited evidence base [32, 33]. This can be provided with or without concomitant psychological interventions ranging from supportive counselling to cognitive behaviour therapy (CBT) [34]. While benzodiazepine tapering and psychological support may minimize withdrawal distress, the duration of such treatment may vary from months to years, which reduces the likelihood of patient treatment compliance and abstinence [18, 35].

Where a severe withdrawal syndrome or other sequelae are anticipated, for instance withdrawal from high doses of benzodiazepines, concomitant drug dependence or comorbid medical problems such as higher pretreatment anxiety and depression, personality pathology, panic disorder diagnosis, inpatient dose tapering for 2 to 4 weeks or longer is usually recommended [27]. These treatment programmes are frequently not cost effective because completion rates and subsequent abstinence rates are often low. One study found that only 10 of 44 patients undergoing either fixed or symptom triggered dose taper completed an 8 day inpatient taper protocol and were benzodiazepine free at the time of discharge [36]. Poor outcomes associated with dose taper regimen have triggered interest in pharmacotherapeutic interventions for the management of benzodiazepine withdrawal symptoms. These include antidepressants, β-adrenoceptor blockers, gabapentin (and pregablin) and anticonvulsants (see [33, 37] for a review). As yet no pharmacotherapy is registered for the treatment of benzodiazepine dependence or withdrawal. However

increasing interest has been devoted to the $GABA_A$ benzodiazepine receptor antagonist (neutral modulator), flumazenil [38].

Competitive benzodiazepine receptor antagonist (neutral modulator) – flumazenil

The imidobenzodiazepine flumazenil (Ro 15–1788) acts as a specific benzodiazepine antagonist (neutral modulator) [39]. Although it is readily absorbed after oral administration, flumazenil is metabolized by the liver with less than 25% systemic availability after first pass hepatic metabolism. Accordingly, its major mode of administration has been i.v., where its clinical effects are evident for only 30–60 min, it being almost entirely eliminated by hepatic metabolism within 60 min [40]. Flumazenil has been shown to have high pharmacokinetic variability resulting in great individual deviation in plasma concentrations [41]. Blood flumazenil concentrations from therapeutic doses are very low, requiring an extremely sensitive assay to measure accurately [42]. Primary indications for the use of flumazenil have been the management of suspected benzodiazepine overdose, and the reversal of benzodiazepine sedative effects associated with general anaesthesia or diagnostic or therapeutic procedures [43, 44].

Flumazenil and the management of benzodiazepine withdrawal

Bolus intravenous flumazenil infusion

A number of studies from the 1990s indicated a role for flumazenil in the management of persistent withdrawal symptoms following cessation of benzodiazepine use. These researchers used dosages of between 1.0 and 2.0 mg flumazenil administered bolus i.v. over 1 to 3 h to manage persistent or re-emerging withdrawal symptoms following cessation of benzodiazepine use [45, 46]. Lader & Morton [45] reported that flumazenil alleviated persistent withdrawal symptoms in patients who had been benzodiazepine free for from 1 month to 2 years, and suggested that the recurrence of symptoms indicates the need for repeated and ongoing flumazenil doses for a longer term to control persistent withdrawal symptoms. Similarly, Saxon *et al*. [46] reported that flumazenil reduced withdrawal symptoms in high dose benzodiazepine dependent patients who had been abstinent from benzodiazepines for a minimum of 3 weeks (but up to 3 years).

More recently, a randomized, placebo controlled study compared multiple bolus i.v. infusions of low dose flumazenil (1 mg/4 h twice daily for 8 days) used in conjunction with oxazepam tapering, to oxazepam taper and placebo in the treatment of benzodiazepine withdrawal. The flumazenil group had a significant reduction in benzodiazepine withdrawal symptoms, reduced craving, increased completion of withdrawal and reduced post detoxification relapse rates [47]. Quaglio *et al*. [48] reported case series data on 29 patients treated with i.v. flumazenil 1.35 mg day^{-1} with clonazepam for 7 days. All patients finished the treatment programme and at 6 months 51% were abstinent from clonazepam taper. Lugoboni *et al*. [49] reported non-peer reviewed data on 286 patients treated with i.v. flumazenil 1–2 mg day^{-1} for up to 8 days with clonazepam taper. Although achieving extremely positive results the authors cautioned of an increased risk of seizure.

Continuous delivery of i.v. flumazenil

While multiple bolus i.v. infusions of flumazenil can reduce withdrawal sequelae [47] or reduce longer term symptoms in the months following withdrawal [45, 46] the low oral bioavailability and very short half-life of flumazenil potentially limit its use in clinical settings and also its usefulness for the prevention of long term withdrawal symptoms.

To address these limitations, Hood *et al*. [50] delivered i.v. flumazenil, 2 mg/24 h in a continuous manner for 96 h (4 days) with oxazepam tapering (total dosage flumazenil 8 mg) to manage symptoms of acute benzodiazepine withdrawal [50]. This extension of Gerra's infusion methodology [47] theoretically results in prolonged, consistent and increasing levels of benzodiazepine receptor occupation throughout the course of treatment. Visual analogue scales of cognitive, physical and craving symptoms as well as measures of mood and anxiety remained essentially stable throughout the infusion and post-infusion phases with a trend to improvement at >72 h (3 days).

These data provide prima facie evidence of the effectiveness of multiple bolus or continuous i.v. infusion of flumazenil in (i) alleviating long term withdrawal symptoms and (ii) preventing clinically significant acute benzodiazepine withdrawal syndromes.

Continuous delivery of subcutaneous flumazenil

Notwithstanding positive clinical outcomes, continuous i.v. flumazenil administration over several days is associated with a number of technical and clinical features that reduce its clinical utility. In particular the requirement to obtain and ensure maintenance of venous access requires specialized medical care which is labour intensive, while patient use of an i.v. pump and line for 96 h restricts movement and may cause discomfort, with the possibility of induction of benzodiazepine withdrawal if the venous line is compromised. These technical issues potentially limit the applicability and access to continuous i.v. flumazenil infusion as a treatment and may be a disincentive for the benzodiazepine dependent person to remain in treatment.

An alternative mode of delivery that avoids these limitations is s.c. administration. However, commercially

available pharmaceutical preparations of flumazenil (e.g. Anexate®, Roche Pharmaceuticals) used in previous studies typically have a pH of around 4.0 making it acidic and unsuitable for s.c. administration. Earlier experience with continuous i.v. flumazenil infusion [50] indicated that treatment with continuous s.c. flumazenil infusion for at least 3 days would be necessary, and possibly longer if protracted withdrawal symptoms were evident. In order to minimize the likelihood of irritation around the infusion site Hulse *et al*. [51] therefore used a flumazenil formulation with a pH of 6.8. In this study 23 (44% male) subjects (mean age 39 years, SD 9.6) with a history of long term benzodiazepine use (11.9 years, SD 7.8) were treated with a s.c. flumazenil solution containing 16 mg flumazenil infused over a 92 h period: 4 mg 24 h^{-1} period (±20%). The flumazenil infusion was augmented with a rapid dose taper oxazepam regimen of 60 mg at baseline, 30 mg at 24 h and 15 mg at 48 h. Study findings indicated that tissue reactivity around the infusion site was mild indicating good local biocompatibility, with mild to moderate benzodiazepine withdrawal symptoms observed even where high dose benzodiazepine use was recorded at treatment entry.

Study data suggested that flumazenil administered by the s.c. route might have equitable clinical benefits to i.v. administration but be superior in that it requires less clinical monitoring and is likely associated with less equipment problems (i.e. dislodged or blocked i.v. needle/line) and adverse events (i.e. venous tissue irritation). These advantages as well as improved patient mobility over the treatment period will also likely result in increased patient satisfaction.

Following s.c. flumazenil administration blood plasma concentrations were evident from day 1 indicating bioavailability. It is likely, however, that monitoring of increased flumazenil GABA receptor occupancy and not flumazenil blood concentrations and their association with physical and psychological withdrawal sequelae are the key to determining optimal concentrations of flumazenil. Despite availability of receptor occupancy data associated with bolus i.v. flumazenil delivery [52], no data are available on receptor occupancy associated with continuous s.c. or i.v. flumazenil infusion. Studies that further explore changes in receptor occupancy and their relationship to withdrawal sequelae including physical and psychological sequelae will undoubtedly help advance this area.

This small proof of concept study indicated that s.c. flumazenil infusion has excellent tolerability, efficacy and improvement on measures of psychological distress. Given this technique is less invasive and requires less staff resources compared with i.v. administration it may prove a significant asset in the management of benzodiazepine withdrawal. Despite these promising findings no direct comparison exists between these two methods (i.v. *vs.* s.c.) of flumazenil infusion (see Table 2 for summary). Recent reports raising concerns over heightened seizure risk during flumazenil assisted benzodiazepine withdrawal [53] highlight the need for randomized controlled clinical trials of these procedures.

Long term management: depot flumazenil

While recent bolus and continuous i.v. or s.c. data have indicated a likely efficacy for flumazenil in the management of acute benzodiazepine withdrawal, this work largely ignores the earlier focus of the ability of flumazenil to manage persistent or re-emerging withdrawal symptoms following cessation of long term benzodiazepine use [45, 46].

Table 2

Summary of reported use of flumazenil in the treatment of long term withdrawal symptoms and management of acute withdrawal

Author	Design	Treatment	Results
Lader & Morton 1992 [45]	Pilot study n = 11	1–2 mg bolus doses over 3 h	Flumazenil successful in alleviating long term symptoms of benzodiazepine withdrawal
Saxon *et al* 1997 [46]	Double-blind pilot n = 10	1.0 mg total in five doses over 1 h × 2	Flumazenil successful in alleviating long term symptoms of benzodiazepine withdrawal
Gerra *et al* 2002 [47]	RCT flumazenil *vs.* oxazepam taper n = 50	1 mg 4 h^{-1} infusion twice daily for 8 days with oxazepam taper	Flumazenil group had significantly reduced withdrawal symptoms, improved programme completion and reduced relapse rates
Hood *et al*. 2009 [50]	Case series/open trial n = 16	2 mg 24 h^{-1} continuous i.v. infusion with oxazepam. tapering for 4 days	Patients had reduced withdrawal symptoms; successfully completed withdrawal. I.v. infusion problematic
Quaglio *et al* 2012 [48]	Case series n = 29	1.35 mg day^{-1} continuous i.v. infusion with clonazepam for 7 days	All patients completed the withdrawal programme with 51% abstinent at 6 months
Hulse *et al* 2012 [51]	Case series n = 23	4 mg 24 h^{-1} continuous s.c. infusion with oxazepam taper for 4 days	Subjective withdrawal symptoms well managed. High patient acceptance. Improvement on measures of psychological distress over withdrawal period

Note: Table includes peer reviewed published data – Lugoboni *et al*. (2011) [49] not included.

An additional clinical challenge, therefore, is to address the high relapse rates (with various estimates between 49% and 57% [54, 55]) that continue to plague long term withdrawal management. This may involve the long term administration of flumazenil over several weeks or months. In this respect use of i.v. or even s.c. infusion may be an impractical method for this long term flumazenil delivery. Given good s.c. tissue compatibility observed by [51] one possible solution is the development of sustained release depot flumazenil formulation. Indeed a pilot flumazenil implant proof of concept safety study has already been undertaken both *in vitro* in a water bath and *in vivo* in sheep.

In vitro flumazenil implant water bath data Recently GoMedical Industries Australia developed an Implant using flumazenil which was formulated as polymer-bound (poly (D-L) lactide) microspheres and compressed into tablets and either coated (long acting) or non-coated (short acting) with a poly (D-L) lactide outer coat. Each uncoated tablet weighed approximately 22 mg and contained approximately 33 mg of flumazenil (16.2%). This reflects similar technology previously employed to develop a long acting sustained release 1.7 g naltrexone implant for the management of heroin dependence that has been shown to sustain blood naltrexone concentrations above 2.0 ng ml^{-1} for approximately 6 months [56].

Preliminary *in vitro* water bath data indicate that non poly (D-L) lactide coated tablets released an average of 2.92 mg (SD 1.46) flumazenil day^{-1} with 66.6% of the 33 mg flumazenil released by day 9 suggesting a possible release life approaching 14 days. This daily release rate is not that dissimilar from daily dose concentrations employed in conjunction with low dose oxazepam by Gerra *et al*. [47] or Hood *et al*. [50] to manage acute benzodiazepine withdrawal. In contrast poly (D-L) lactide coated tablets released 0.23 mg (SD 0.045) flumazenil day^{-1}. Assuming viability of the poly (D-L) lactide base this suggests this tablet will continue to release flumazenil for approximately 140 days. This is not unfeasible given similar stability shown by poly (D-L) lactide naltrexone implants developed by this group. Notwithstanding this, approximately 10 tablets would be required to achieve flumazenil release of 2.3 mg day^{-1}. Such levels are however not inconceivable in humans with 20 naltrexone poly (D-L) lactide coated tablets of the same diameter commonly inserted subcutaneously to manage heroin dependence.

In vivo sheep tissue flumazenil implant biocompatibility study In a step closer to human trials preliminary assessment of biocompatibility following s.c. flumazenil implantation in sheep has also been undertaken (University of Western Australia Animal Ethics RA/4/100/362). Sheep were implanted subcutaneously with either A) a single poly (D-L) lactide uncoated flumazenil tablet (fast release), B) a single poly (D-L) lactide coated flumazenil tablet (long release), C) 10 poly (D-L) lactide uncoated flumazenil tablets; or D) 10 poly (D-L) lactide flumazenil coated tablets. All tablets were inserted by a bevelled syringe applicator into subcutaneous tissue in the abdomen just below the lateral midline through a 7–10 mm incision which was then sutured. The site of incision and implant were then monitored for redness, swelling, tenderness or exudation at days 1, 3, 7 and then weekly to 6 months with animals sacrificed at 6 months and biopsy of the entire implant site histologically examined. No major serious adverse events were noted during the 6 month monitoring period and histological examination showed typical end stage response of mild inflammation and histopathology consistent with wound healing for both single and multiple tablet animals regardless of coating, suggesting that the majority of tissue reaction is associated with the polymer not flumazenil release.

Future research

How does flumazenil work as a treatment for benzodiazepine withdrawal symptoms? It is intriguing that a compound that is used acutely in clinical settings to reverse benzodiazepine intoxication effects rapidly (and hence, potentially precipitate benzodiazepine withdrawal) and in research settings in bolus infusion as a specific panicogen [57, 58], has utility in lower dosage, and subacute usage as a therapy to aid benzodiazepine withdrawal [50, 51]. Although the exact mechanism is not completely understood, we can offer the following observations. Firstly, although flumazenil is traditionally regarded as an antagonist at all receptor subtypes, it actually has partial positive allosteric modulatory activity at $GABA_A$ receptors containing the α_6 subunit [59]. Exposure to flumazenil appears to reverse observed chronic benzodiazepine uncoupling *in vivo* quickly [60], and as mentioned above there is now a large body of evidence demonstrating that long term exposure to benzodiazepines (at least in animal models) induces a change in $GABA_A$ subunit composition [14, 15, 17]. It may thus be that this specific $GABA_A$ subunit combination is of especial utility in enabling transition towards the benzodiazepine state whilst minimizing classical withdrawal symptoms. Secondly, it is apparent from our research [50, 51, 57, 58] that the clinical effects of flumazenil vary substantially with dose and rate of infusion. This is congruous with research into the anxiolytic effects of novel neuropeptide compounds that do not always follow a linear dose–response curve, that sometimes require high baseline stress or triggers to exert an effect, or are non-responsive to existing animal models of anxiety. Clarification of flumazenil's mechanism of action is an active area of research interest.

Flumazenil may have a number of other possible indications including the management of withdrawal associated with physical dependence on alcohol [61, 62] and

amphetamines [63]. In 2005, the pharmaceutical group Hythiam applied for US patents for the use of flumazenil for these indications.

Non-substance abuse research has indicated that a high rate bolus infusion of flumazenil (2 mg in 10 min) can act as a specific panicogen in subjects with acute serotonin-depleted [64] panic disorder [57, 58], but not in persons with social anxiety disorder [65] or alcohol dependence [62]. Flumazenil infusions are not usually anxiogenic in non-anxious controls, in patients with other anxiety disorders, or even in patients with remitted panic disorder [66]. The mechanism by which high rate bolus flumazenil infusion can induce panic symptoms in susceptible individuals is unknown. One key hypothesis is, however, that flumazenil 'resets' the benzodiazepine receptor set point that is shifted in the inverse agonist direction by chronic use of benzodiazepines [67]. Thus, it is prudent for clinical studies of flumazenil to monitor for emergent anxiety symptoms.

Recent preclinical research suggests that the action of flumazenil can vary according to the presence of other $GABA_A$ modulators. Flumazenil appears to function as a low efficacy, neutral $GABA_A$ modulator at low doses and in the presence of benzodiazepines such as diazepam, but at higher doses or intriguingly when given in combination with a positive $GABA_A$ modulator acting at a non-benzodiazepine site (e.g. neuroactive steroids) it exhibits the properties of a partial agonist (low efficacy, positive $GABA_A$ modulators) [68]. The effects of concomitant GABAergic agents warrant careful consideration, as patients with benzodiazepine dependence commonly use other psychoactive substances, and flumazenil treatment protocols may include co-prescription of decreasing doses of benzodiazepines or other drugs to alleviate withdrawal symptoms.

Conclusion

Despite the adverse effects of long term prescribing, benzodiazepine prescribing and use continues to escalate. This is largely because no superior alternative pharmacotherapeutic treatment has been developed to treat anxiety and insomnia. Benzodiazepines are fast acting and at least on initial prescribing are safe and predictable in their effects. It is possible that flumazenil may not only have application in the management of benzodiazepine withdrawal but may be able to manage some of the adverse iatrogenic effects and development of tolerance which occur with long term use. Savic *et al*. [52] demonstrated that it was possible to reverse the tolerance to anti-convulsant effects of benzodiazepines. Further, rats treated with flumazenil along with a benzodiazepine do not develop tolerance but still apparently experience an anxiolytic effect [69]. Flumazenil has been demonstrated to have positive effects on mood, memory, cognition and motor performance in both humans [70, 71] and animals [72–76]. Slow delivery of low dose flumazenil either via subcutaneous implant or transdermal delivery via creams or patches may be able to control or 'mop up' the iatrogenic adverse effects that accompany long term benzodiazepine use [51] thus revolutionizing the way this class of drugs is used and prescribed.

Competing Interests

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