Flumazenil and naloxone are considered to be pharmacologically ideal antidotes. By competitive binding at the molecular target receptors, they are highly specific antagonists of two important drug classes, the benzodiazepines and opioids, respectively. Both antidotes enjoy rapid onset and short duration after parenteral administration, are easily titrated and are essentially devoid of agonist effects. Yet only naloxone is widely used as a component of the ‘coma cocktail’, a sequence of empirical treatments to correct altered mental status, while experts discourage the use of flumazenil for such patients. This review contrasts the history, indications, published evidence and novel applications for each antidote in order to explain this disparity in the clinical use of these ‘ideal’ antidotes.

Introduction

The quest for the ideal antidote has its origins in antiquity, and helped define the discipline of pharmacology. Indeed, the science of antidotal therapy has advanced in step with an improved understanding of the mechanism of action and toxicity of various natural and synthetic drugs. Perhaps the two best examples of pharmacologically pure antidotes are naloxone and flumazenil. These highly specific antagonists inhibit the noxious effects of two important drug classes (the opioids and the benzodiazepines) by competitive binding at their respective target receptors, and are essentially devoid of agonist effects. As such, these antidotes are generally regarded as exemplars of the ideal antidote.

It is therefore surprising to many that these two antidotes have experienced widely different uptake into clinical practice. Both enjoy very rapid onset after parenteral administration, and are able to reverse coma caused by either opioids or benzodiazepines quickly. Their effects are rapidly titratable, specific and relatively short in duration, allowing both diagnostic and therapeutic use. Yet only naloxone has retained its place on the so-called ‘coma cocktail’, the short list of empirical treatments to be considered when treating altered mental status of unknown cause [1, 2]. Only naloxone is on the World Health Organization core list of essential medicines. Recently, as one element of the public health response to an epidemic of opioid overdose, programmes have appeared to allow bystanders to carry and administer naloxone before the arrival of paramedics, circumventing the usual barriers to access a prescription medicine like naloxone. Flumazenil, on the other hand, carries a ‘black box’ warning in the United States. Experts recommend against widespread use, restricted to very narrow indications or only on the recommendation of a medical toxicologist [3–5] while discouraging empirical administration as part of a ‘coma cocktail’ [1, 2, 6]. To understand this discordant practice requires understanding how these antidotes differ, and the modern approach to the unconscious overdose patient.

Flumazenil

Pharmacology

Flumazenil (Ro 15–1788) is an imidazobenzodiazepine, developed by Hoffmann-La Roche in the 1980s. A structurally similar investigational agent (Ro 15–4513) developed at the same time held promise as an antidote to ethanol, but only flumazenil has been approved for human use. Flumazenil has a very rapid onset of action after parenteral administration, and competitively antagonizes the sedating effects of a wide range of benzodiazepines such as midazolam, diazepam and lorazepam at the GABA_A receptor. It can also reverse
the effects of structurally dissimilar sedatives which also bind to the benzodiazepine binding site, namely the cyclopyrrolone zopiclone, the pyrazolopyrimidine zaleplon and the imidazopyridine zolpidem. On the other hand, it does not reverse the effects of other GABAergic sedative/hypnotics such as barbiturates, inhalational anaesthetics, propofol or ethanol, nor does it reverse the effects of opioids. This specificity is not inversely given these latter agents have different binding sites on the receptor. The high affinity binding site for flumazenil is found on the extracellular surface of the GABAA receptor at an interface between the α and γ2 subunits, in close proximity to the benzodiazepine binding site [7]. An increasing awareness of the complexity of subunit subtype combinations which make up the pentameric GABAA receptor helps explain ligand selectivity/resistance, dependence/withdrawal and other clinical effects. The predominant receptor composed of α1 mediates sedation and muscle relaxation, those with α2 or α3 anxiolysis and anticonvulsant effects and the extrasynaptic receptor with α5 amnesia [8]. Flumazenil is therefore considered a neutral allosteric modulator at the benzodiazepine site, with selective antagonism at α1 and partial agonism at α2, α3 and α5 subtypes. Its pharmacological properties are summarized in Table 1.

Approved indications and dosing

In the United Kingdom, flumazenil carries the following label: ‘indicated for the complete or partial reversal of the central sedative effects of benzodiazepines. It may therefore be used in anaesthesia and in intensive care... For diagnosis and treatment of intoxications or overdose with only or mainly benzodiazepines’. The label continues ‘Contraindications... In mixed intoxications with benzodiazepines and tricyclic and/or tetracyclic antidepressants, the toxicity of the antidepressants can be masked by protective benzodiazepine effects... (in) severe intoxication with tricyclics/heterocyclics, flumazenil should not be used...’. Similar approved indications for treatment of overdose and warnings exist in the United States and other countries.

Flumazenil is typically administered as 0.2 mg by intravenous push (pediatric dose 10 μg kg⁻¹), every 1 to 2 min, until reversal of excess sedation or 1 mg total dose (paediatrics 50 μg kg⁻¹). Because the duration is relatively short, close monitoring is needed following reversal, especially if the duration of effect of the agent being reversed is longer than flumazenil.

Clinical experience

Although efficacious at reversing sedation due to benzodiazepines, the primary concerns in clinical use from the outset were also related to flumazenil’s mechanism of action, and therefore its ability to induce abrupt benzodiazepine withdrawal, including seizures and agitation. Although these effects may be relatively short-lived, the presence of flumazenil also renders their usual treatment (i.e. benzodiazepines) problematic. Furthermore, many intentional overdoses involve multiple drugs, and the benzodiazepine may well be antagonizing the stimulant or proconvulsant properties of a co-ingested agent. In this scenario, reversing the beneficial effects of the benzodiazepine is harmful. Such concerns were vindicated when, within a few years of introduction into clinical practice and prior to US FDA approval, cases of ventricular tachycardia and death in mixed overdoses involving amitriptyline, [9] dothiepin [10] and chloral hydrate [11] had been reported in the British Medical Journal.

Table 1

Comparison of pharmacologic properties of flumazenil vs. naloxone

<table>
<thead>
<tr>
<th></th>
<th>Flumazenil</th>
<th>Naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU EINCEC/EINCS List</td>
<td>not listed</td>
<td>207–365–7</td>
</tr>
<tr>
<td>Chemical name</td>
<td>4 H-imidazo(1,5-a)(1,4)benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester</td>
<td>morphinan-6-one, 4,5-epoxy-3, 14-dihydroxy-17-(2-propenyl)-, (5alpha)-</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C₁₅H₁₄FN₃O₃</td>
<td>C₁₉H₂₁NO₄</td>
</tr>
<tr>
<td>Molecular weight (daltons)</td>
<td>303.3</td>
<td>327.4 (363.8 as naloxone HCl)</td>
</tr>
<tr>
<td>log P (octanol/Water)</td>
<td>1.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>~0.17</td>
<td>very low (high first pass metabolism)</td>
</tr>
<tr>
<td>Volume of distribution (l kg⁻¹)</td>
<td>0.95</td>
<td>2.7</td>
</tr>
<tr>
<td>Time to effect after intravenous administration (min)</td>
<td>onset 1–3, peak 6–10</td>
<td>onset 1–2, peak 5–10</td>
</tr>
<tr>
<td>Terminal half-life (min)</td>
<td>40–80</td>
<td>30–80</td>
</tr>
<tr>
<td>Metabolism</td>
<td>hepatic (de-ethylated free acid, glucuronidation)</td>
<td>hepatic (glucuronidation)</td>
</tr>
<tr>
<td>Target receptor</td>
<td>GABAₐ₄</td>
<td>μ (μ₁, μ₂) opioid</td>
</tr>
<tr>
<td>IC₅₀</td>
<td>~0.5 nM (bovine)</td>
<td>43 nM (μ, human)</td>
</tr>
<tr>
<td>Kᵢ</td>
<td>0.09 nM (bovine)</td>
<td>0.25 nM (μ, human)</td>
</tr>
</tbody>
</table>
The reported experience over the next decade attempted to establish criteria for identifying patients at low risk of seizure and withdrawal amongst the larger population of unconscious overdose patients. In a single centre review of patients given 0.4 to 0.8 mg flumazenil mostly by pre-hospital physicians for coma attributed to drug overdose, five of 35 seized, of whom two had multiple seizures. However, when the authors attempted to identify and then to apply low risk criteria retrospectively to the cohort, only four of the 35 would have been classified as being low risk. All five patients who seized had been using benzodiazepines chronically, but each patient also had at least one other high risk feature [12]. In a randomized clinical trial of consecutive unconscious patients in whom benzodiazepine overdose could not be excluded at presentation, 3/53 patients allocated to 1 mg flumazenil intravenously over 3 min developed agitation, and 1/53 who had co-ingested maprotiline and had a wide QRS complex developed a systolic blood pressure of 60 mmHg [13]. By 1997, a selective summary of the published experience with mixed overdose patients identified ‘aggression, agitation’ following flumazenil administration in 14/245 (6%) of cases, although the risk of seizure appeared to be lower with more selective use [14]. In a prospective study using more careful titration (50 μg over 15 s, repeated every 3 min as needed, to a maximum of 1 mg) to reverse coma due to mixed sedative ingestion, agitation, vomiting and/or sinus tachycardia were observed in four of 25 subjects [15]. In summary, the propensity for flumazenil to precipitate seizures and acute withdrawal, combined with the expected favourable outcome when benzodiazepine overdose is treated supportively, resulted in recommendations for highly selective use [2, 3, 5] ideally under the care of a medical toxicologist [4].

A meta-analysis of seven randomized clinical trials from six countries of adults treated in the emergency department or intensive care unit with 1–2 mg flumazenil (242 subjects) vs. placebo (210 subjects) for suspected drug or benzodiazepine overdose reported a number needed to treat of 2.2 (95% CI 1.9, 2.7) for reversal of coma favouring flumazenil, offset by a number needed to harm of 16 [12, 23] for any adverse effects, including both seizures (reported in a single subject, yielding a non-significant relative risk of 2.9 (95% CI 0.1, 69)) and minor effects (e.g. anxiety, vomiting) [16]. There was insufficient information from the trial reports to test whether the use of flumazenil reduced subsequent investigations, interventions or resource utilization. More recently, a larger meta-analysis which included an additional six randomized trials involving a total of 994 emergency patients with suspected or verified benzodiazepine overdose obtained more precise risk estimates [17]. Of note, eight patients allocated to flumazenil had an arrhythmia and three seized, for a number needed to harm of 50 (95% CI 29, 180) for a serious adverse event. The number needed to harm for any adverse event (including agitation, dysphoria and vomiting) was 6.2 (95% CI 4.8, 8.6). Two large poison centre datasets, one in California [18, 19] and the other in the UK [5] have reported a relatively low incidence of seizures (14/1067 pooled) even when flumazenil was administered to patients who had previously seized (0/7) or had also reportedly overdosed on a proconvulsant drug (8/336). None of the 83 patients younger than 12 years of age reportedly seized [18]. These datasets, however, are limited by incomplete clinical information and ascertainment of outcomes.

The experience with overdose patients must be contrasted with the use of flumazenil for reversal of excessive sedation following iatrogenic administration of benzodiazepines for diagnostic or therapeutic procedures, which represents a very different population [3, 20]. An expert panel recommending antidote stock for US hospitals concluded that the ‘primary use (of flumazenil) is for iatrogenic overdose’ [1]. Reversing a known therapeutic dose of a parenterally administered, short acting benzodiazepine is rather different from an oral overdose of multiple unknown drugs for self-harm. Any history of benzodiazepine dependence, prior seizure disorder and concurrent medications is generally known before the patient is sedated, but can only be suspected in the unconscious overdose patient. Perhaps not surprisingly, while seizures can still occur, their incidence is estimated to be quite low. Resedation remains a concern [3, 20] especially if flumazenil reversal is used to expedite discharge. A theoretical concern also exists regarding the ability of an antagonist like flumazenil to delay the development of within-dose tolerance, the main mechanism whereby one recovers from a benzodiazepine overdose [21].

Other emerging indications for flumazenil include the treatment of the rare, so-called ‘paradoxical responses’ to intravenous midazolam [22] that occur during procedural sedation, in which disinhibition leads to agitation and disruptive behaviour during the loading phase. Flumazenil has a non-specific analgetic effect, resulting in awakening during propofol [23] or sevofluorane [24] general anaesthesia. It can reverse residual depression of diaphragm function more than 24 h after several days of continuous midazolam infusion for mechanical ventilation in the ICU [25]. More provocative is a recent report of its use in expert hands to diagnose and treat delirium several days after hospital admission for severe alcohol withdrawal treated with high dose benzodiazepines (median dose lorazepam 120 mg + diazepam 145 mg) [26, 27] or, paradoxically, for the chronic management of benzodiazepine dependence [28].

**Naloxone**

**Pharmacology**

Naloxone is a synthetic derivative of oxymorphone developed by Sankyo in the 1960s, in which the N-methyl...
group is replaced by an \( N \)-allyl group. The active levorotatory enantiomer is a nearly pure competitive antagonist at the \( \mu \), \( \delta \) and \( \kappa \) opioid receptors [29]. Thus, it competitively antagonizes the effects of both endogenous peptide ligands (e.g. enkephalins, endorphins and dynorphins) as well as opioid xenobiotics (e.g. morphine, fentanyl and heroin), yet does not by itself cause respiratory depression even at high doses. Its affinity for the \( \mu \) receptor is approximately an order of magnitude greater than for the \( \kappa \) receptor, and two orders of magnitude greater than for the \( \delta \) receptor [30]. Its pharmacological properties are contrasted with those of flumazenil in Table 1.

The onset of action is very rapid after parenteral administration and its duration of action is usually less than 1 h. Naloxone is typically injected intravenously or intramuscularly with nearly similar onset of action when including the delay to obtaining intravenous access [31, 32]. Naloxone undergoes extensive first pass metabolism primarily via glucuronidation in the liver, and therefore its oral bioavailability is very low. When needleless routes are preferred, it can be administered by nebulization into the pulmonary tree [33] and small volumes can be atomized intranasally [34]. When volumes approach 1 ml/nostril, however, a substantial fraction of intranasal naloxone is swallowed or expelled, reducing bioavailability and efficacy [34–38]. Only two routes of administration are discouraged: orally and direct pulmonary instillation via an endotracheal tube.

The low oral bioavailability of naloxone has resulted in two interesting pharmacologic applications when coformulated with other opioids intended for oral administration. First, coformulation with the partial agonist buprenorphine discourages illicit diversion since injecting the oral formulation will precipitate acute withdrawal. Second, because oral naloxone binds to \( \mu \) receptors in the enteric nervous system, it reduces the adverse effects of oral opioids on gastrointestinal motility, especially constipation and post-operative ileus [39].

Approved indications and dosing

Naloxone is used diagnostically and therapeutically for the reversal of respiratory depression presumed to be due to natural opiate or synthetic opioid overdose. Its only adverse effect is the ability to induce abrupt opioid withdrawal when given at too high a dose in opioid-dependent patients [40]. Because many patients who overdose on opioids are opioid-dependent, excessive doses targeting complete reversal should be avoided. However, opioid-dependent patients also develop tolerance. The potential for high tolerance combined with variation in opioid potency makes it difficult to estimate the dose of the culprit opioid being antagonized, rendering initial dose selection and subsequent titration somewhat nuanced.

Importantly, irrespective of the availability of naloxone and during its titration, non-pharmacological approaches to treating respiratory depression take precedence. Rescuers should not simply rely on the antidote in patients with severe respiratory depression without first performing basic measures including clearing the airway and assisting ventilation [40]. Ventilation and oxygenation by bag-mask-valve has the highest priority, and will allow an opportunity for careful titration of naloxone over several minutes to the point of reversing respiratory depression. Understandably, such dose titration can be difficult for inexperienced healthcare providers managing a life-threatening overdose, or when intravenous access is not available. Nevertheless, the pulmonary complications associated with naloxone reversal from apnoea may be attributable at least in part to abrupt pharmacologic reversal without adequate anatomical support of the airway and positive-pressure ventilation [32, 35, 41].

An excessive dose of naloxone in an opioid-dependent patient induces immediate opioid withdrawal, which is both highly unpleasant for the patient and can cause a behavioural emergency with some risk to rescue personnel. There is growing awareness that widely recommended initial doses of 0.4 mg to 2 mg are unnecessary, and that 40 \( \mu \)g is a more appropriate initial dose in most cases [35, 40]. Subsequent doses can then be rapidly escalated up to 2 mg based on effects on respiratory effort. The relatively short duration of naloxone can be both a proverbial blessing (when withdrawal has been induced) and curse (when the patient is allowed to refuse transport to hospital or to leave hospital ‘against medical advice’ without considering the risk of recrudescence). Opioid withdrawal, either pharmacological or due to abstinence alone, can cause seizures in the newborn period, so naloxone should only be used with care in the first few days of life when the mother has been opioid dependent.

Clinical experience

The safety and efficacy of naloxone are well established both in clinical practice and in the reported literature. For example, investigators in Florence reported excellent survival from respiratory arrest in a retrospective study of 126 consecutive heroin overdose patients treated by the physician-staffed mobile ICU during a 4 year period [42]. Acute lung injury or other complications were rare, and there were four survivors to hospital discharge in the seven out-of-hospital cardiac arrests with asystole as the presenting rhythm. Their treatment protocol emphasized endotracheal intubation and intravenous administration of 0.4 mg naloxone every 3 min as part of the arrest protocol in such cases. In a retrospective 1 year review of the prehospital experience in San Francisco for presumed opioid overdoses (at least three of circumstantial evidence of parenteral drug use, respiratory rate < 6 breaths min\(^{-1}\), cyanosis, Glasgow Coma Scale \(\leq 12\), miosis) due to mostly heroin, 575/609 cases with
signs of life before administration of naloxone improved level of consciousness and increased respirations within 5 min. Of these, 42 required protective restraints, and five ‘escaped from the care of paramedics’. Among the 444 patients taken to a single hospital, four were hypoxic on arrival and were diagnosed with acute lung injury but ultimately did well. However, none of the 16 patients found pulseless (but without advanced signs of death) survived to hospital discharge despite advanced respiratory support and at least 2 mg naloxone [32].

The relatively short duration of naloxone can result in recurrence of respiratory depression when the opioid being antagonized has a longer duration of action. Such recrudescence is rare when reversing parenteral heroin, which has an equally short duration of action [43]. Indeed some prehospital systems have allowed such patients to refuse transport to hospital with apparently few subsequent deaths [44]. One must not, however, extrapolate that safety experience to other opioids, especially methadone and oral overdoses of sustained-release formulations. Experience has confirmed what pharmacology would predict. After naloxone reversal, these patients require admission to hospital and naloxone infusion over many hours to days [2]. A key consideration is, as always, titrating naloxone to reverse the respiratory depression without aiming for a completely awake state and risking withdrawal followed by elopement.

To reduce the risk of occupational needlestick injuries, intranasal atomization of naloxone is used in some prehospital systems. While the time to onset is similar, the lower bioavailability of the intranasal vs intramuscular route likely explains a lower rate of agitation and a greater need for rescue or redosing [37, 38, 45].

More recently, a global epidemic of opioid overdose deaths combined with the safety and efficacy of naloxone and the observation that overdose deaths were often witnessed by friends or family suggested an opportunity for deploying the antidote to future bystanders, allowing administration prior to arrival of the ambulance [37, 46–50]. Many jurisdictions have now reported their experience with so-called bystander naloxone programmes distributing this prescription medication to lay persons most likely to witness an opioid overdose [51]. In the United States, an electronic survey of distribution programme staff estimated a cumulative estimate of approximately 10 000 overdose reversals with naloxone by 2010 [52]. Implementation of an overdose education and prevention programme bundled with naloxone distribution targeting high risk opioid users and their social support workers, family and friends was associated with a modest reduction in opioid overdose deaths in Massachusetts [53] and is likely cost-effective [54]. Antidote delivery mechanisms for these lay programmes include intranasal atomization by syringe or more concentrated nasal spray, and an auto-injector with voice prompts [34].

Barriers to this still-controversial harm reduction strategy vary by jurisdiction and include the many unwitnessed opioid arrests, drug cost, availability and stability considerations, and dispensing of naloxone only by physician prescription. Societal concerns include encouraging escalating drug abuse by creating a false sense of security, and that layperson naloxone administration may replace activation of the prehospital care system, especially in the absence of Good Samaritan legal protection for bystanders who are complicit with illegal drug use [36, 46, 55, 56]. There is increasing evidence from addiction researchers that these latter concerns are ill-founded, yet broader implementation is limited by the practical considerations of training, logistics and cost [57].

The ‘coma cocktail’

Historical background

With this information in mind, one can now consider the concept of a ‘coma cocktail’. Historically, the empirical administration of a sequence of potential reversal agents had its origins in the United States [58]. Motivated in part by an effort to protocolize resuscitation to ensure consistency and to avoid errors of omission, a short list of interventions considered safe and rapidly efficacious was taught to emergency care providers. Hypertonic glucose and oxygen remain key constituents of this approach, given the rapid neurological impairment caused by deficiencies of either of these essential metabolic substrates [2]. Understandably, in an era when endotracheal intubation and ventilator support were in their infancy, physicians also attempted to avert deep coma at all costs. Many overdose patients had ingested potent sedatives such as barbiturates, and aspiration remains a serious complication of many poisonings. Of course, respiratory depression due to opioids has been a fixture of accidental and intentional poisonings for over a century.

As such, analepsis or alertness were once considered to be important safety end points when treating the unconscious overdose patient. A fundamental distinction was lost. The desire to reverse coma was conflated with the importance of providing oxygen, physiologic pH (ventilation) and glucose, followed by other essential supportive measures. Indeed, suggestions in the literature that ‘flumazenil results in complete awakening, with restoration of upper airway protective reflexes, thus enabling gastric lavage to be performed and transfer of the patient from the emergency room to another hospital department’ [14] reflect this antiquated approach and strike the modern reader as antediluvian.

The shift away from analepsis rendered a number of fashionable interventions obsolete. Caffeine, physostigmine and sniffing salts [59] are but three
examples (Table 2). Modern ‘intensive’ care including early endotracheal intubation and advances in mechanical ventilation allowed a transition to supportive care based on a physiologic approach, aided by pharmacologic sedation [60]. And the benzodiazepines became an essential therapy for reducing agitation, stopping seizures, treating hyperthermia and generally supporting an overdose patient, rather than a toxin to be antagonized.

As such, the use of flumazenil was counterproductive [3]. Beyond the desire to maintain or induce sedation, even a modest risk of seizures for the unconscious overdose patient argued against its empirical diagnostic use following intentional overdose [2]. Attempts to identify low risk criteria to improve safety yielded a highly select population, severely limiting its utility [12, 61]. Flumazenil was shown not to be cost-effective in an industry-sponsored, randomized clinical trial of selected overdose patients [61].

One would be wrong to conclude from the above that benzodiazepine overdose is entirely benign. Indeed benzodiazepine use and abuse are prevalent and increasing, with parallel increases in hospitalizations and intensive care unit admissions following overdose [4, 5, 28]. The risk of seizure following flumazenil can also be anticipated in many cases. In particular, the risk of seizure is highest in patients chronically treated with benzodiazepines, following head injury, pre-existing seizure disorder, and patients who have overdosed on a proconvulsant drug, especially a heterocyclic antidepressant [1]. These factors, as well as a QRS interval greater than 100 ms by itself, should be considered contraindications to its use [13]. Notwithstanding expert recommendations against its liberal use, in actual practice flumazenil is undoubtedly being used more often [6, 20, 60]. For example, the vast majority of poisoned patients given flumazenil identified in the UK database over a 2 year period were deemed to have either no indication or a contraindication to its use on expert review, yet complications are uncommon [5]. Young children with deep sedation following accidental ingestions of a benzodiazepine may be one population in which titrated reversal with flumazenil should be considered, since these patients are unlikely to have contraindications or develop seizures [2, 20].

And naloxone? Here the objection to its use in the ‘coma cocktail’ is the implication that it should be used to reverse coma. The much higher lethality of the opioids over the benzodiazepines is due to their propensity to depress respiration, which reflects the different effects of the opioid vs. GABA receptors. As discussed above, the indication for its use is respiratory depression, and the desired end point is restoration of ventilation, not wakefulness. When used as an ingredient of the cocktail approach to coma, one risks its use in patients who are opioid dependent but have a depressed mental status due to any number of other conditions, including neurological emergencies or a non-opioid overdose. In such cases, naloxone will induce withdrawal without improving the mental status, taking a patient from mere coma to coma with vomiting [2]. A better approach is to reserve naloxone for earlier in the alphabetized resuscitation algorithm, to correct ‘B’ for breathing after supporting ‘A’ for airway, rather than correcting ‘D’ for disability (i.e. coma) in a patient with adequate ventilation.

In conclusion, the modern approach to a patient with an altered level of consciousness should not be protocolized, empirical administration of fixed doses with an end point of analepsis, but rather the targeted correction of immediate threats to life. D-glucose corrects hypoglycaemic coma and seizures, identified by point-of-care glucometry. Oxygen is titrated to pulse oximetry, Bradypnoea and central hypoventilation, potentially due to opioids, are appropriate triggers for naloxone (Table 3) [15, 58]. Unlike opioids which cause central apnoea, hypoventilation due to benzodiazepines

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obsolete analeptics no longer used for reversal of coma of uncertain aetiology</strong></td>
</tr>
</tbody>
</table>

| Methylxanthines (caffeine, theophylline) | 
| Physostigmine | 
| Physical stimulation, ice bath | 
| Ammonium carbonate (“smelling salts”) | 
| Amphetamines | 
| Strychnine | 
| Picrotoxin | 
| Nikethamide | 
| Camphor | 

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘Coma cocktail’ of agents to be considered when treating altered mental status of unknown aetiology</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most common indication</th>
<th>Typical initial adult dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextrose (D-glucose)</td>
<td>Capillary blood glucose &lt;5 mmol/L</td>
</tr>
<tr>
<td>Oxygen</td>
<td>Pulse oximetry &lt;92–95%</td>
</tr>
<tr>
<td>Naloxone HCl</td>
<td>Bradypnoea (± miosis)</td>
</tr>
<tr>
<td>Thiamine HCl (vitamin B1)</td>
<td>Prevention of Wernicke encephalopathy in alcoholic or malnourished patients</td>
</tr>
</tbody>
</table>

Br J Clin Pharmacol / 81:3 / 433
is caused primarily by upper airway obstruction [15]. As such, the treatment is airway support including endotracheal intubation when necessary. With both flumazenil and naloxone, even pharmacologically ideal antidotes are no substitute for basic airway management and modern principles of targeted resuscitation and supportive care.

Competing Interests
The author has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the author) and declares no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES
24 Karakosta A, Andreotti B, Chapsa C, Pouliou A, Anastasiou E. Flumazenil expedites recovery from sevoflurane/remifentanil


