65 - Parenteral treatment

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62 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 Acutely disturbed or violent behaviour Acute behavioural disturbance can occur in the context of psychiatric illness, physical illness, substance abuse or personality disorder. Psychotic symptoms are common and the patient may be aggressive towards others secondary to persecutory delusions or auditory, visual or tactile hallucinations. This section deals with behavioural disturbance in the context of severe mental illness. Agitated states caused by illicit substance misuse are dealt with in Chapter 9. The clinical practice of rapid tranquillisation is used when appropriate psychological and behavioural approaches have failed to de-escalate acutely disturbed behaviour. It is, essentially, a treatment of last resort. Patients who require rapid tranquillisation (RT) are often too disturbed to give informed consent and therefore participate in RCTs but, with the use of a number of creative methodologies, the evidence base with respect to the efficacy and tolerability of pharmacological strategies has grown substantially. A comprehensive and up-to-date consensus guideline was published in 20181 and, more recently, a systematic review and meta-analysis.2 A network meta-analysis of RT in the emergency department has also been published.3 Oral/inhaled treatment Several studies supporting the efficacy of oral SGAs have been conducted.4–7 The level of behavioural disturbance exhibited by the patients in these studies was moderate at most, and all participants accepted oral treatment (this degree of compliance would be unusual in clinical practice). Patients recruited to these studies received the SGA as antipsychotic monotherapy. The efficacy and safety of adding a second antipsychotic as a ‘when necessary’ treatment have not been explicitly tested in formal RCTs. A single-dose RCT showed sublingual asenapine to be more effective than placebo for acute agitation.8 The efficacy of inhaled loxapine in behavioural disturbance that is moderate in severity is also supported by RCTs.9–11 The use of this preparation is now restricted in many countries owing to the risk of bronchospasm. Dexmedetomidine, an α2 receptor agonist used in anaesthesia, has been developed as a sublingual film. It seems to be rapidly effective in acute agitation.12 Parenteral treatment Large, placebo-controlled RCTs support the efficacy of IM preparations of olanzapine, ziprasidone and aripiprazole. When considered together, these trials suggested that IM olanzapine is more effective than IM haloperidol, which in turn is more effective than IM aripiprazole, which itself is more effective than ziprasidone.2,13,14 The level of behavioural disturbance in these studies was moderate at most and differences between treatments small. A large observational study supported the efficacy and tolerability of IM olanzapine in clinical emergencies (where disturbance was severe).15 A study comparing IM haloperidol with a combination of IM midazolam and IM haloperidol found the combination more effective than haloperidol alone for controlling agitation in palliative care patients.16

Schizophrenia and related psychoses CHAPTER 1 Several RCTs have investigated the effectiveness of parenteral medication in ‘real-life’ acutely disturbed patients. Overall: ■ ■Compared with IV midazolam alone, a combination of IV olanzapine or IV droperidol with IV midazolam was more rapidly effective and resulted in fewer subsequent doses of medication being required.17 ■ ■IM midazolam 7.5–15mg was more rapidly sedating than a combination of haloperidol 5–10mg and promethazine 50mg (TREC 1).18 ■ ■Olanzapine 10mg was as effective as a combination of haloperidol 10mg and promethazine 25–50mg in the short term, but the effect did not last as long (TREC 4).19 ■ ■A combination of haloperidol 5–10mg and promethazine 50mg was more effective and better tolerated than haloperidol 5–10mg alone; 6% of patients had an acute dystonic reaction (TREC 3).20 ■ ■A combination of haloperidol 10mg and promethazine 25–50mg was more effective than lorazepam 4mg (TREC 2).21 ■ ■A combination of IM chlorpromazine 100mg, haloperidol 5mg and promethazine 25mg was no better than IM haloperidol 5mg plus promethazine 25mg (TREC Lebanon).22 ■ ■A combination of IV midazolam and IV droperidol was more rapidly sedating than either IV droperidol or IV olanzapine alone. Fewer patients in the midazolam– droperidol group required additional medication doses to achieve sedation.23 ■ ■IM olanzapine was more effective than IM aripiprazole in the treatment of agitation in schizophrenia in the short-term (at 2 hours) but there was no significant difference between treatments at 24 hours.24 ■ ■IM midazolam 5mg was faster acting and more effective than olanzapine 10mg, ziprasidone 20mg and both 5 and 10mg haloperidol in a large (n = 737) emergency room study.25 ■ ■In an open-label study, the combination of IM haloperidol and IM lorazepam was found to be similar in efficacy to IM olanzapine.26 ■ ■IM droperidol and IM haloperidol were equally effective.27 ■ ■IM droperidol with IM midazolam was more effective than IM haloperidol with IM lorazepam.28 Nearly 10 years ago, Cochrane concluded that haloperidol alone is effective in the - management of acute behavioural disturbance but poorly tolerated, and that co- administration of promethazine (but not lorazepam) improves tolerability.29,30 However NICE considers the evidence relating to the use of promethazine for this purpose to be inconclusive.31 The authors also stated that ‘haloperidol used on its own without something to offset its frequent and serious adverse effects is difficult to justify’.32 A systematic review and meta-analysis of IM olanzapine for agitation found IM olanzapine and IM haloperidol to be equally effective, but IM olanzapine was associated with a lower incidence of EPSEs.33 Cochrane suggests that droperidol is effective and may be used to control disturbed and aggressive behaviours caused by psychosis.34 Droperidol has seen a resurgence in use in some countries having become available again (its initial withdrawal was voluntary, so reintroduction is not prohibited).

64 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 1 In a meta-analysis that examined the tolerability of IM antipsychotics when used for the treatment of agitation, the incidence of acute dystonia with haloperidol was reported to be 5%, with SGAs performing considerably better.35 Acute EPSEs may adversely affect longer-term compliance.36 In addition, the formal prescribing information in most countries for haloperidol calls for a pretreatment ECG37,38 and recommends that concomitant antipsychotics are not prescribed. The mean increase in QTc after 10mg IM haloperidol can be up to 15ms but the range is wide.39 Promethazine may inhibit the metabolism of haloperidol;40 a pharmacokinetic interaction that is potentially clinically significant given the potential of haloperidol to prolong QTc. While this is unlikely to be problematic if a single dose is administered, repeat dosing may confer risk. Droperidol is also associated with QT changes (the reason for its withdrawal). In an observational study set in hospital emergency departments, of the 1,009 patients administered parenteral droperidol, only 13 patients (1.28%) had an abnormal QT after dose administration. In seven of these cases, another contributory factor

was identified. There were no cases of torsades de pointes (TdP).27 In all RT studies of IM droperidol, the overall rate of QTc measurements greater than 500ms was less than 2%.2 Intravenous treatment is now rarely used in RT but where benefits are thought to outweigh risks it may be considered as a last resort. A small study comparing highdose IV haloperidol with IV diazepam found both drugs to be effective at 24 hours.41 Two large observational studies have examined the safety of IV olanzapine when used in the emergency department. The indications for its use varied, agitation being the most common. In one study,42 in the group treated for agitation (n = 265), over a third of patients required an additional sedative dose after the initial IV olanzapine dose. Hypoxia was reported in 17.7% of patients and supplemental oxygen was used in 20.4%. Six patients required intubation (two of these because of olanzapine treatment). In the other study,43 IV olanzapine (n = 295) was compared with IM olanzapine (n = 489). Additional doses were not required for 81% of patients in the IV group and 84% of patients in the IM group. Respiratory depression was more commonly observed in the group receiving IV olanzapine. Five patients in the IM group and two in the IV group required intubation. In an acute psychiatric setting, ‘high-dose sedation’ (defined as a dose of more than 10mg of haloperidol, droperidol or midazolam) was not more effective than lower doses but was associated with more adverse effects (hypotension and oxygen desaturation).44 Consistent with this, a small RCT supports the efficacy of low-dose haloperidol, although both efficacy and tolerability were superior when midazolam was co-prescribed.45 These data broadly support the use of standard doses in clinical emergencies but the need for further physical restraint after lower doses needs to be considered. A small observational study supported the effectiveness of buccal midazolam in a PICU setting.46 Parenteral administration of midazolam, particularly in higher doses, may cause over-sedation accompanied by respiratory depression.47 Lorazepam IM is an established treatment and TREC 221 supports its efficacy, although combining all results from the TREC studies suggests that midazolam 7.5–15mg is probably more effective. More recent studies have used 5mg IM midazolam and found it to be rapidly effective.28,48 A Cochrane review of benzodiazepines for psychosis--induced aggression and agitation concluded that most trials were too small to highlight differences in either

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