Long-acting antipsychotic medication, restraint and treatment in the management of acute psychosis

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Objective: Zuclopenthixol acetate (ZA) is the first parenteral antipsychotic medication introduced for clinical use in the treatment of aggression and agitation that has a relatively prolonged duration of action. The aim of this paper is to explore a number of important ethical and clinical issues that are raised by the use of this novel therapeutic formulation.
Method: Relevant literature is explored and several issues are identified from which arguments for and against the use of medication of this type are raised. These issues are considered in general and with the use of a number of stylised clinical scenarios.
Result: The use of long-acting antipsychotic medication is complicated by its impact upon patient autonomy, by considerations of informed consent and by the need to provide justice to all patients and staff in a psychiatric treatment setting. The use of ZA in the emergency treatment of psychotic patients may only be justified under specific clinical circumstances and its use is not appropriate as routine chemical restraint.
Conclusions: Zuclopenthixol acetate is a novel and potentially useful treatment alternative in the acutely disturbed patient. Institutions in which ZA is used in emergency settings should develop protocols to guide clinicians in its appropriate use and provide monitoring.
Key words: emergency treatment, ethics, restraint, sedation, zuclopenthixol acetate.

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Zuclopenthixol acetate (ZA) (Clopixol-Acuphase) is a novel antipsychotic formulation. It has a unique duration of action such that, when administered as an intramuscular injection, it has clinical effect for a period of several days. This property, along with its substantial sedative effects, has contributed to its use and promotion in the short-term management of agitated or aggressive psychotic patients. As such, ZAis the only currently available example of a relatively long-acting medication that is used in clinical practice as a form of restraint. Its use has raised a number of therapeutic, ethical and legal issues that will be the focus of this paper. Although this paper will refer specifically to ZA throughout, the arguments raised may well apply to any medication with similar clinical properties that may become available in the future.

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Clinical background

Zuclopenthixol is a thioxanthene derivative that binds primarily to dopamine D_1, D_2, $5HT_{2a}$ and α_1-adrenergic receptors. It is available in three formula-

tions: as a tablet, as a long-acting depot (zuclopenthixol decanoate) and as a shorter-acting depot (zuclopenthixol acetate). The pharmacokinetics of ZA are such that it reaches peak serum concentration 24–48 h following an intramuscular injection. The levels gradually fall from this time and are at approximately one-third of the peak level at 72 h [1]. In the one *in vivo* study of the mechanism of action of ZA, it was found that within this period zuclopenthixol acts to block a high proportion of dopamine D_2 receptors in striatum [2]. This is consistent with the proportion of dopamine receptor blockade that is usually associated with antipsychotic efficacy in typical neuroleptics [3–5]. A number of open studies have demonstrated a reduction in Brief Psychiatric Rating Scale [6] scores during the 3-day period of action, including scores on psychotic items such as hallucinatory behaviour and unusual thought content [7,8]. This is not consistent with the generally accepted time frame for onset of antipsychotic effect and may reflect general sedation or the methodology of these open studies more than an actual amelioration of psychotic symptoms.

Zuclopenthixol acetate is used in the management of acutely disturbed patients with psychotic disorders such as schizophrenia. The commonly used dose ranges from 50 to 150 mg in a single injection that may be repeated after 24 h if insufficient response has been achieved. Current prescribing guidelines recommend that ZAshould not be used for more than 2 weeks and no more than 400 mg (in a maximum of four injections) be administered. Sedation is achieved rapidly, usually within 15–30 min. The peak effect is at approximately 8 h post injection. This effect is dose-dependent and in most patients persists for up to 3 days [9].

Several studies have been conducted that have compared the use of ZAin acutely disturbed patients with standard therapy [10,11], although concerns have recently been raised as to the depth of this research [12]. A review recently published by the Cochrane group failed to find any substantial evidence that ZA offers advantages over standard treatment [13]. The majority of published studies have tended to find a similar clinical response with ZAand a control medication (oral or intramuscular haloperidol). Patients receiving ZAreceived fewer injections and experienced greater sedation in several studies. Concerns raised about the possibility of a high incidence of extrapyramidal side effects associated with high dopamine D_2 occupancy [3] were partially borne out with higher rates in patients treated with ZAthan with comparison medication in some studies [11] but not all [14]. Whilst it is noticeable that the trials of ZAare limited, it is important to consider the substantial difficulties in performing studies in acutely disturbed patients and to consider the results both of these studies but also the open reports previously mentioned.

Although not fully borne out by the aforementioned studies, there appear to be a number of potential therapeutic benefits to the administration of ZA that relate to the reduction in the number of parenteral injections required during a fixed period of time. These include: (i) a reduction in traumatic muscle injury; (ii) a reduction in psychological trauma associated with physical restraint required during the administration of parenteral medication; (iii) a reduction in the incidence of physical injury to both patients and staff, including reduction in the incidence of needle stick injury; and (iv) a reduction in ‘breakthrough’ symptoms of agitation and episodes of aggression. Alternative management strategies often will involve waiting until symptoms re-emerge prior to the subsequent re-administration of a sedating medication. These symptoms are likely to be distressing in themselves as well as place the patient and others at risk of harm.

There has been little systematic evaluation of these potential advantages although one study indicated that ZAmay offer a cost savings by reducing nursing time required for the management of agitated patients [15]. It appears reasonable to assume that reducing the number of injections received by patients will lower the number of staffing injuries as the time of administration of parental medication is one of significant risk for nursing staff [16].

Inadequately treated aggressive symptoms will have an impact upon the patients, other patients, visiting family and staff. The aggressive patient is at risk of physical injury, of harming others (and experiencing future legal sanctions) and a period of ‘out of control’behaviour which may have substantial negative psychological impact upon the patient’s self-image and perception of his or her illness as something he or she can manage and bring under control. This may lead to denial or repression of the illness experience and affect future compliance. Additionally, the experience of receiving repeated parenteral medication for sedation is likely to be experienced as an assault and to invoke images of punishment and incarceration for the patient rather than those of therapy and relief. This may include the development of posttraumatic symptomatology [17].

There are, however, clinical concerns with the administration of a long-acting medication to an acutely disturbed patient. Any idiosyncratic or dose-related side effects will be experienced for a longer period of time than had a shorter-acting agent been administered and the patient may not experience relief from these until the medication effects have subsided. The history available from a disturbed patient may be unreliable and if this is not available from another source, comorbid physical illnesses may be overlooked. Performing a physical examination on a patient prior to administration of the sedating medication may also be impossible. In addition, it may not be possible to exclude the use of illicit substances either as the cause for the disturbed behaviour or as a coexisting problem. Both the presence of substance use or physical illness may raise concerns about the safety of administering a parenteral neuroleptic and the prolonged half-life ensures that any adverse consequences of doing so will be relatively prolonged.

Ethical issues

A number of ethical concerns have been raised about the use of ZA [18]. These concerns have presented in the context of the use of ZA to sedate or control patients experiencing disturbed behaviour and the legal framework under which this practice is controlled. There are concerns in regards to the effect ZA will have on patient autonomy, as well as concerns in regards to the balance between the rights of an individual patient versus the rights of others (staff and other patients) around him/her. Several of these issues arise due to a lack of clear distinction between the use of ZA as a form of chemical restraint as distinct from treatment.

Impact upon autonomy

One of the primary concerns with ZA relates to its capacity to affect patient autonomy over a relatively prolonged period of time. This argument states that the sedation and modulated mental state produced by ZA will remove the patient's free capacity to make decisions, to refuse consent or to appeal a determination of incapacity. The medication may temporarily affect cognitive functioning as well as conscious arousal and the patient will lose the opportunity to regain control of him or herself for up to 3 days. This duration of action appears not to be in keeping with the use of the medication to control a discrete episode of disturbed behaviour. The imposition of sedative effects for several days is also not the least restrictive means with which control of an episode of behaviour may be achieved and is therefore problematic.

Opposing this stance is the argument that patients have a right to receive the best available treatment and that denying patients this treatment option may result in adverse clinical consequences. Additionally, it may be argued that the continuous action of ZA over several days is much more likely to return the patient's capacity and autonomy rather than fluctuating treatment that may result in the periodic re-emergence of agitation and aggression. It may restore already compromised autonomy rather than remove or impair it despite temporarily limiting the patients' freedom of behaviour. Finally, it may be argued that while the duration of action is not consistent with a treatment being the least restrictive option, the administration of fewer injections with ZA does in some way meet this standard.

A conflict of rights

A further ethical issue that may be considered relevant concerns the rights of other patients to be provided with a safe and therapeutically beneficial environment. Additionally, the staff who care for patients have the right to be provided with a safe work environment. Both of these conditions are more likely to be achieved if timely and effective sedation is provided to disturbed patients. It may be argued that in reducing the need for repeated injections, ZA will reduce the injuries experienced by staff. No member of society, and no patient in hospital, is able to exercise absolute freedom and limits may be seen as appropriate in the balance for 'overall good'. Interestingly, where this has been addressed legally, the courts have recognised that there is a need for a patient's right to liberty to be balanced with an institution's duty to protect the patient and others from the consequences of acts of violence [19]. Unfortunately, one of the most influential of decisions in this area considered the use of seclusion and mechanical restraint but not the use of involuntary medication [20].

Informed consent, restraint and treatment

As with any medication, issues associated with the provision of informed consent are crucial in the appropriate use of ZA. If a patient is able to give informed consent, its use is unproblematic. However,

the capacity of a patient to provide informed consent in an emergency or a state of agitation is likely to be limited. In some jurisdictions, such as that of the province of Ontario in Canada, provisions exist for consent to be provided by a substitute decision-maker following a determination of incapacity. This may be possible in some circumstances but emergency sedation is usually required rapidly and contact with a third party will frequently be impractical. This poses the question of how best to protect the rights of the patient while not hindering the provision of acute care needed for the safety of the individual and others. Legally this has been addressed in a variety of ways. One of these is to distinguish between restraint (which may not require consent) and treatment (that does). By distinguishing between these two concepts, it is possible to define an argument that clearly states that the use of ZA, without informed consent, is problematic. In its simplest form this argument states:

(1) There is a significant and definable difference between restraint and treatment. Restraint (physical or chemical) is an act performed in an emergency situation to prevent harm to a patient or others and as such may occur without informed consent. It should constitute the minimal use of the force required. Treatment, however, is a process directed at the illness experienced by the patient and always requires consent from the patient or a defined substitute decision-maker.

(2) Parenteral medication used in an emergency is a legitimate form of chemical restraint.

(3) The duration of action of ZA is such that it acts beyond the time appropriate for restraint and as such is better conceptualised as a treatment.

(4) Zuclopenthixol acetate should not be prescribed or administered without informed consent and therefore should not be used routinely as a chemical restraint.

The crucial issue here appears to be whether it is legitimate and useful to distinguish between restraint and treatment. Attempts to do so have appeared within the law and within mental health legislation although noticeably these distinctions are not commonly represented in current Australian mental health legislation. For example, in Ontario, the Mental Health Care Act (1996) defines restraint as, 'to place under control when necessary to prevent serious bodily harm to the patient or to another person by the minimal use of such force, mechanical means or chemicals as is reasonable having regard to the physical and mental condition of the patient'. Treatment (in the Health Care Consent Act) 'means anything that is done for a therapeutic, preventative, palliative, diagnostic, cosmetic or other health related purpose'. The Victorian Mental Health Act (1986) defines treatment in relation to a mental disorder as, 'things done in the course of the exercise of professional skills to—(a) remedy the mental disorder; or (b) lessen its ill effects or the pain and suffering which it causes'. Restraint is not defined, although there is a specific section in the act on the use of mechanical restraint. The use of medication as chemical restraint is not addressed. Likewise, the Queensland Mental Health Regulations (1985) define restraint in terms of 'mechanical means' without reference to medication, although this definition appears to separate restraint from what would be considered standard treatment.

Clearly, mechanical restraint (and the use of seclusion with which it is usually considered) appears to be different from treatment. The distinction of restraint from treatment has been legally explored: for example, in an important case in Massachusetts [21], psychiatrists in a university hospital were charged with the use of seclusion in non-emergency situations. The judge in the case found that the use of seclusion in non-emergency circumstances was an administrative sanction and not a treatment. This decision has led to a reconsideration of the indications for the use of seclusion and restraint, and principles under which these interventions may be used have been defined [22,23]. Criteria for the use of these interventions include the acute control of violence, for the containment of destructive impulses and to provide isolation from the demands of interpersonal relatedness and sensory stimulation.

Mechanical restraint appears to only be acceptable when it comprises the minimal use of force required to prevent harm coming to a person or persons. In these circumstances, the treating team are acting under the principle of beneficence, to do good (by acting to prevent harm), while temporarily compromising the patient's freedom. Mechanical restraint would be applied only when a patient's capacity to act autonomously is compromised by the effects of mental illness. The use of restraint in this way may also be justified by considering the principle of justice, in particular the right of other patients to receive equitable, safe and reasonable treatment. The provision of restraint is not undertaken with the intention of acting in accordance with what the patient, when calm and competent, would be likely to choose given the circumstances. The act of restraint

does not alter the course of the illness and the illness is not the direct target of the intervention.

Restraint appears to differ from what we would commonly consider treatment but the distinction is less clear when we consider treatment undertaken in an emergency situation. Emergency treatment is not uncommonly provided without informed consent in certain circumstances in areas of medicine other than psychiatry. For example, emergency surgery may be undertaken to save the life of an unconscious patient without consent if there is no available relative to provide substitute consent. A decision to undertake treatment would be based predominately upon the principles of beneficence. In these circumstances, the treatment is considered to be provided in what is regarded as the 'best interests' of the patient or in such a way as to be consistent with what a 'reasonable' patient would be likely to choose. There are similarities in the circumstances of an unwilling and acutely disturbed psychotic patient. Usually, in these circumstances, treatment may be provided where the patient has been deemed incapable to refuse (or give) consent to treatment. Consent provided by a substitute decision-maker is considered to be most ethically appropriate if it is given as an expression of what the patient would be likely to choose rather than what is deemed by others to be in the patients' best interests. It is not always possible to represent these ideas, however, and often decisions are made on the standard of 'best interests'. In both the circumstances of the unwilling incapable patient and the unconscious patient, the provision of treatment directly has an impact upon the course of the illness and it is the illness that is the focus of the intervention.

Is the use of medication to manage an acutely disturbed patient more closely analogous to the use of mechanical restraint or to the example of emergency medical care? In that the aggression or agitation may be seen as secondary to the illness, we may consider that the use of medication in this way is at least treating a manifestation of the illness; this would be consistent with the Victorian Mental Health Act definition of treatment; to 'lessen its ill effects'. More specifically, however, there is no evidence that the use of parenteral antipsychotic medications in a disturbed patient will alter the long-term course of the illness, as these medications work over a time course of weeks rather than hours. Additionally, disturbed behaviour rather than the actual illness is the focus of the intervention.

There does not appear to be a clear demarcation between the notions of restraint and treatment when applied in these circumstances. To move forward, I believe it is necessary to consider in more detail some of the clinical circumstances in which the dilemma may be resolved. To do this, I will consider two clinical possibilities while acknowledging from the outset that there will be a difficult grey area between these ends of the spectrum of clinical presentation.

First, we will consider the majority of patients who present requiring the use of a sedative or restraint. These patients will clinically improve with the administration of one or perhaps a few doses of standard short-acting treatment (such as parenteral haloperidol). They may continue to experience psychotic symptoms but the problematic behaviour will be controlled or resolve. In these patients, it is reasonable to consider that restraint is the focus of the intervention and that this should be done in the least restrictive manner. The use of ZA would not be appropriate in these circumstances. The use of medication in these circumstances is closely analogous with the use of mechanical restraint for the control of violence.

The second circumstance is one that appears to occur uncommonly and in a minority of patients. In this circumstance, a patient presents with persistent agitation associated with the relapse of psychosis. A patient may have presented repeatedly in this fashion over the course of a number of episodes of relapse and have demonstrated persistent agitation despite the use of repeated doses of standard treatment in each episode. It is difficult to estimate the proportion of disturbed patients who fall into this category. However, we can get some indication from research on the use of seclusion as a method of responding to disturbed behaviour. Anumber of studies of seclusion practices have found that the average duration of seclusion use tends to be low (e.g. a mean length of 10.8 h and a median of 2.8 h in one study [24]). These studies indicate, however, that a small group of patients with persistent disturbed behaviour require seclusion for extended periods of time (up to 120 h in the study by Soloff and Turner [24], up to 72 h in a study by Binder [25]) or may require repeated periods of seclusion. Additional evidence is found in studies of parenteral sedation such as that of Baastrup *et al*. [10]. In this study, patients treated with intramuscular haloperidol or zuclopenthixol (not ZA) required up to 12 injections over 6 days, although the mean number of injections was quite low (1.1–4.0 for various patient subgroups). This indicates that there appears to be a small group of patients in whom the use of a longer-acting medication would be useful.

The presentation of persistent disturbed behaviour in these circumstances often appears closely related to the psychotic disorder and as such does not present as an isolated incident to which restraint may apply in isolation from treatment. Zuclopenthixol acetate would appear to be appropriate in these circumstances as it would be directed towards the treatment of the episode of disturbed behaviour in conjunction with the underlying psychosis. There are several goals of treatment with ZAin these circumstances: to restore patient autonomy by ameliorating both psychosis and agitation; to act in the interest of the patient to relieve distress and provide protection; and to provide justice to staff and co-patients by providing a safe environment and timely treatment. The use of ZAas a treatment in these circumstances is analogous with the use of seclusion or restraint as 'treatment' as defined by some authors [22,23]. This distinction refers to the use of restraint in certain circumstances where the target of the intervention is the amelioration of ongoing aggression associated with psychosis rather than the acute control of violence.

In the second scenario described, the use of ZA appears consistent with notions of treatment rather than just restraint. As a treatment, however, concerns about the provision of informed consent (by a substitute) still exist and may be legally mandated in some jurisdictions. If this were the case, it would seem appropriate for a short-acting medication to be initially administered to allow time for consent for ZA treatment to be obtained from a third party. This would also allow the patient opportunity to gain self control if the episode differs in nature from those seen previously, as well as allowing the initiation of an appeal of incapacity or involuntary status.

Clinical suggestions

Ethical difficulties with the use of ZA would appear to be most satisfactorily resolved by the limitation of its use to specific clinical circumstances in which the following criteria are satisfied: (i) the prior establishment of a diagnosis of a psychotic disorder, such as schizophrenia, that is not secondary to substance intoxication/withdrawal or a general medical condition; (ii) a previous history of similar agitated or violent behaviour that required treatment with parenteral medication, seclusion or physical restraint for a period of at least 24 h; and (iii) some clinical indication that the present disturbed behaviour is related to a relapse of the psychotic illness.

Attempts to obtain informed consent (from the patient or substitute decision-maker) should always be made. Where this is not possible immediately, the use of a short-acting medication to 'buy time' to allow a substitute to be contacted should be considered. Where the use of a substitute decision-maker is not local practice, a judgement should be made considering: (i) any views previously expressed by the patient or substitute decision-maker; (ii) the degree of physical and emotional trauma involved with the administration of parenteral medication to the particular patient (the risks to the patient and staff); (iii) the acceptability of other alternatives to the patient and the risks associated with these; and (iv) the likelihood that the targeted behaviour will respond to alternative medication with a shorter duration of action.

In addition to these concerns, ZA should only be used where there is adequate monitoring for the detection of extrapyramidal or other side effects. The rationale for its use, target symptoms and the response of target symptoms should be carefully documented. It would seem appropriate that institutions in which ZAis used develop protocols for the formal assessment of disturbed behaviour and the response of patients to ZA. This may prevent the repeated administration of the medication to patients in whom clear benefit is not evident. Finally, as with all difficult clinical decisions, obtaining a second opinion or consultation should be considered.

Conclusion

Zuclopenthixol acetate is a novel and potentially useful treatment alternative. Its use raises a number of clinical and ethical issues. These issues revolve around concerns for the autonomy of patients, the rights of other individuals who deal with and are in contact with disturbed patients and the right of patients to be able to provide (or have others provide in their interest) informed consent to treatment. Adequate resolution of these issues requires careful analysis of both the ethical arguments and specific clinical issues. The use of ZAis appropriate in certain clinical circumstances but should occur only following careful individual and institutional consideration.

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