Depot antipsychotics in psychiatric practice - An overview

Dr. P. N Suresh Kumar
MD, DPM, DNB, PhD
Associate Professor of Psychiatry, KMCT Medical College, Calicut, Kerala, India

Maintenance drug therapy is an important aspect of the treatment programme of patients with schizophrenia. Unfortunately a substantial number of schizophrenic patients are either irregular in taking prescribed medications or discontinue therapy of their own. Depot neuroleptics were developed in 1960s in an attempt to improve long-term treatment of psychiatric patients (and potentially other disorders benefitting from long-term antipsychotic medications). Depot drugs, as distinguishable from shorter acting intramuscularly administered agents can provide a therapeutic concentration of at least a seven day duration in one parenteral dose. The depot antipsychotic are esters formed between alcohol group of the drug and a long chain of fatty acids (enantic, decanoic, palmitic, undecylenic acid), and this ester is dissolved in oil (sesame oil or viscoleo). Antipsyhcotics in themselves are fat soluble, but the esterification increases this fat solubility a thousand fold, the longer the carbon chain, the more solubility is increased.

The ester is released from the oil phase by slow diffusion into the body water phase. The higher the fat solubility, the slower the release. Upon release from the oil, the ester is either immediately hydrolyzed or distributed to other tissues and then hydrolyzed. The goal is to obtain a sufficiently constant delivery of the drug from the depot, so that the serum level is kept constant as possible between the injections.

Fluphenazine enanthate was the first depot neuroleptic approved for use in the US in 1963. Sooner it was replaced by fluphenazine decanoate because of fewer side effects and longer duration of action. Flupenthixol decanoate was started available in Europe since 1967. Haloperidol decanoate was started available in Europe in 1981 and in US in 1986 (Knudsen, 1985). Recently Zuclopenthixol decanoate (Wistedt et al, 1991) and long acting risperidone injection (Parellada et al,

2010) has been found to be useful in the maintenance treatment of schizophrenia. A long acting injectable formulation of olanzepine received not-approvable letter from the US FDA owing to idiosyncratic over sedation (FDA, 2008).

Advantages

The long-acting injectable depot neuroleptics were introduced to overcome a number of theoretical and clinical problems in the management of psychosis particularly in maintenance treatment. They are mainly:

1. Parenteral administration allows the drug to bypass deactivating process in the intestine and liver by first pass metabolism, thereby providing more predictable and constant plasma levels (Comaty & Janicak, 1987). Because of the same reason depot neuroleptics are indicated for patients who are refractory to oral agents or who have been repeatedly hospitalized while taking oral neuroleptics.

2. Another advantage is that there is less interindividual variability in the relationship between dosage administered and blood level achieved when medication is administered parenterally (Nayak et al, 1987).

3. Many antipsychotics need serum levels above a lower critical level to achieve antipsychotic response. This is influenced by factors such as absorption, food, other drugs like anticholinergics etc. Parenteral administration bypasses all these factors. Depot medications may be associated with more uniform blood levels, and hence fewer adverse effects than those associated with daily dosing and multiple dosage peaks.

4. It provides a measure of control over the medication prescribed and confirmation that medication is actually received by the patient, thereby reducing the risk of non compliance. More over guardians require to persuade patients to receive their medication only once a month instead of every day.

In British studies, non compliance over a 6 week period was reported to be as high as 60% with oral neuroleptics (Jonson, 1990), and as low as 20% over a 2 year period with depot neuroleptics (Jonson et al, 1973). Six double blind random assignment, prospective studies compared the relapse rate of patients on oral and depot preparations and the average difference in relapse rates between two treatments was 15%, favoring depot drugs (Glazer & Kane, 1992). When the data from these studies were combined using the Mantel-Haenzel statistical test, a highly significant different was evident, favoring depot drugs (Davis et al, 1989).

Major side effects

Despite the attractiveness of this treatment option, many psychiatrists are reluctant to use this treatment method. Anecdotal reports indicate that in US only 10% -20% of neuroleptics involve

depot form compared with as much as 50% in the UK. The reason for this difference is the assumption of high incidence of adverse reactions with depot neuroleptics.

Neuroleptic Malignant syndrome

In retrospective studies (Addonizio et al, 1986), case control studies (Keck Jr et al, 1989) and prospective studies (Keck Jr. et al, 1991) there was no evidence that the risk for NMS is high in patients on depot neuroleptics. In fact, the great majority of reported NMS cases involve oral neuroleptics and there are no data to suggest that prior history of NMS would be a contraindication to the use of depots in whom this method offered potential advantages.

Tardive dyskinesia

TD is an important concern in the long-term use of neuroleptics. Kane et al (1986) reported an incidence of 4% -5% per year, with no evidence that depot drugs were associated with greater risk than with oral neuroleptics. Kane & Smith (1982) in a reanalysis of three previous studies concluded that the association between TD and depot drugs could be due to that patients on depot drugs are strong drug compliers thereby produce a cumulative increase in the dose received. The Yale Tardive Dyyskinesia Study (Morgenstem et al, 1990) also indicate that depot administration had no effect on the incidence of TD. These data indicates that only randomized, prospective, controlled doubled blind trials of first time neuropetic treated patients with depot and oral neuroleptics only can assess the relative risk for TD with these two modes of administration.

Extrapyramidal Symptoms

Some early studies reported higher frequencies of akinesia associated with depot fluphenazine than with oral preparation (Rifkin et al, 1977). Glazer (1984) in an analysis of 8 controlled studies concluded that the risk of developing EPS is 1.5 times greater with depot fluphenazin than with oral neuroleptics. Same author in 1992 in a reanalysis of 4 studies using Mantel Haenzel test found that the risk of developing EPS is 25% with depot than with oral forms, this difference was marginally significant. However there are many confounding factors in these type of analyses viz. comparison of higher depot doses with lower oral doses, comparison of piperazine class depot with non-piperazine class oral neuroleptic, systematic bias, inconsistent method of measuring EPS etc.

A Canadian study found that when oral haloperidol was switched to depot haloperidol only one out of 41 patients developed frank extrapyramidal symptoms. It has been reported that stable levels of depot haloperidol are lower than stable oral level which may explain the lower risk of EPS with depot haloperidol (Erenshefsky, 1990)

Injection site reactions

The first report of injection site reaction was with depot fluphenazine enanthate (Tetreault et al, 1969). A few instances of pain, edema and palpable mass at the injection site have been reported to the manufacturer of fluphenazine decanoate injections (personal communication, Squibb ER & Sons Inc., Princenton, N.J., June, 1990). Haloperidol decanoate induced skin reactions were reported by Hamann et al in 1990 and De Cuyper et al in 1986 because of subcutaneous injection. There was no details about dose (s), site (s) or technique of intramuscular injection but possible reason assumed was inadvertent injection of glass particles.

Fluspirilene as an acqueous suspension has been found to cause subcutaneous nodules months after injection which may be due to direct toxicity of concentrated fluspirilene particles in microcrystalline form (Lapierre et al, 1979).

Injection site reactions can be avoided by rotating the injection site, administering deep intramuscular than subcutaneous injection and limiting the volume. A modified Z-track method has been recommended for injection of depot neuroleptics (Knudsen, 1985; Belanger, 1982).

Physician's perception of therapy

Often physicians have negative attitudes towards parenteral administration. In fact, practitioner's own biases and negative thoughts about depot route get conveyed to the patient resulting in poor patient acceptance. Physician may also want to save the patient from the fear and pain of injection and often associate depot drugs with non complaint or bad patients (Glazer & Kane, 1992). In reality, the clinical experience suggest that the vast majority of patients will accept depot medication if the clinician discusses the advantages and disadvantages over a period of time.

Patient's perception of therapy

Till date this aspect has not been specifically studied. However many patients prefer injections to having to taking pills (Diamond, 1983). Patients who deny their illness may be more comfortable with monthly or bimonthly injection than remembering to take drugs daily. Others may consider injection as intruding or disregarding; some may fear the pain of intramuscular injection. Glazer et al (1987) in a comparison of intramuscular versus subcutaneous injection reported more leakage with intramuscular and less pain with subcutaneous injection.

Guidelines for the use of depot neuroleptics

Dosage

It should be individually tailored and kept under constant review partly because of development of tardive side effects and partly because the dose required will come down with control of symptoms. Initially stabilize the patient on lowest effective oral dose.

Usual dosage conversion is 10mg/day fluphenazine =12.5mg/2 wks depot.

10mg/day haloperidol = 100-200mg/4wks depot

8-10mg/day flupenthixol = 40mg/2 wks depot

Supplementation with oral drugs may be necessary for the first few months till optimal dosage requirement is determined.

It has been estimated that the dose can be reduced by half over the first year of maintenance therapy and a further 25% during the second year. At the beginning of maintenance therapy half of patients require fluphenazine decanoate every 2 weeks, at the end of 12 months, 1/3 require every 3 weeks and 1/3 every 4 weeks or less frequently (Johnson, 1982). Kane et al (1979) suggested that doses as low as 1.25-5.0mg every 2 weeks will be effective in some patients. High dose group have been found to have more akinesia and E.P.S.

Techniques of Injection

Depot antipsychotic injections are normally given by deep intramuscular injection into the upper outer quadrant of the buttock, thus avoiding the sciatic nerve (Fig 1). The lateral side of the thigh or the deltoid muscle are alternative, but less satisfactory injection sites (in the latter case, beware of the circumflex nerve) (Belanger & Chouinard, 1982)

a) Ensure the needle is of adequate length (a minimum of 4 cm is recommended)

b) Wipe the injection site with alcohol and allow to dry otherwise alcohol may infiltrate subcutaneous tissue causing local irritation.

c) Z- tracking technique: Using the thumb, apply a shearing stress to the skin so that the skin and the subcutaneous tissue slide over the underlying muscle. Inject through the displaced skin with a smooth action (Figure 2).

d) Do not allow the hilt of the needle to touch the skin, as occasionally violent movement could cause the needle to break at the base.

e) If resistance is felt, it probably indicates contact with the ileum and the needle should be withdrawn 1-1.5cm

f) As with oily injections, it is important to ensure, by aspiration before injection, that inadvertent intravascular injection does not occur.

g) Using a 2 inch needle, inject no more than 3cc of medication per injection into the upper quadrant of buttock.

h) After drawing medication, draw a small air bubble of 0.1cc into the syringe and change the needle for injection.

i) Inject medication including air bubble which forces last drop from needle into the muscle and prevents any medication from being deposited in subcutaneous tissues as needle is withdrawn.

j) Wait for 10sec before withdrawing the needle, then do so quickly and release skin. After full depression of the plunger the needle is withdrawn and the shearing force to the skin

simultaneously released (Fig.3)

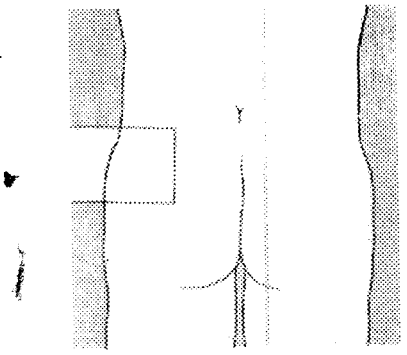
k) Do not massage injection site, as this may force medication to ooze from muscle and infiltrate subcutaneous tissues.

l) Precaution should be taken with glass ampoules to avoid injection of glass particles.

m) Injections should be alternated between two sides and never be given through the same puncture hole as a previous injection

n) The patient should be encouraged to exercise the limb

Fig-1



Fg-2

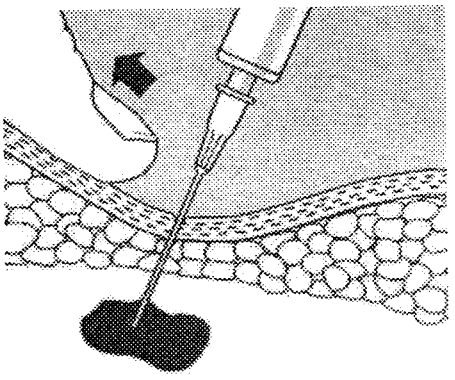
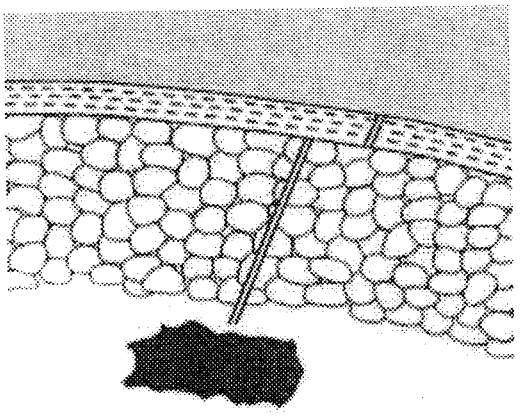


Fig-3



Selection of depot preparation

Available injectable depot preparations are as follows:

Fluphenazins

- Decanoate
- Enanthate

Zuclopenthixol decanoate

Zuclopenthixol Acetate

Haloperidol decanoate

Fluspirilene

Risperidone long acting injectable

Paliperidone palmitiate

Olanzepine palmoate

Iloperidon Depot

Their therapeutic effects as well as side effects are broadly similar to oral forms. Depot preparations have similar efficacy and toxicity. Given a correct adjustment of dose, their antipsychotic action is equal. Differences centre on the relative side effects profile. Fluphenazine

decanoate has longer duration of action where as fluphenazine enanthate produces more E.P.S. Fluphenazine decanoate and zuclopenthixol decanoate are the most sedative preparations used in patients with overactivity, aggression or elation of mood. Action of zuclopenthixol depot last for 1 week. Fluspirilene is without any sedative effect. Controlled and uncontrolled studies have found that flupenthixol is useful in apathetic, autistic and depressed patients with schizophrenia (Trueman & valentine, 1974) and has efficacy against negative symptom compared with other classical antipsychotics like fluphenazine, haloperiodol and chlorpromazine.

Medico-legal concerns

There are no data to suggest that a physician incurs greater liability with one route of neuroleptic administration than with other. The essential issue is physician should meet the standard of care in dealing with patients which include prudent weighing of indications for medication, periodic monitoring for side effects and informed consent.

Depot antipsychotic therapy: stretching the limits

Siegel et al (2002) described an antipsychotic drug delivery system which may allow half-yearly or even yearly dosing. For clinical application, a small, disc shaped implant will be necessary. The disc will be about the size of a coin. It can be inserted under the skin and held in place with a single suture. The entire surgery can be conducted under local anesthesia, and is likely to last less than 15 minutes. Removal of disc is expected to be equally quick and easy. The delivery system can be designed to release a steady dose of the drug for up to a year. Surgical implants of antipsychotic drugs carry two advantages: a longer duration of action and the possibility of removal of the implants should unacceptable adverse events arise (in case of depot antipsychotics injections, removal of the injected drug is not possible).

Indian studies

Till date there are only three studies reported (Varma & Kulhara, 1989; Agarwal & Sharma; 1994; Fermandez et al 1999) assessing the efficacy of depot antipsychotics in Indian setting. Of these first 2 were about haloperidol decanoate in schizophrenia and the third was about zuclopenthixol in psychotic population. All the three studies reported significant clinical efficacy with favourable side effect profile.

Conclusion

Considerable progress has been made over the past decade in further elaborating the benefits and risks of maintenance treatment of psychosis. Of these the corner stone is long-acting injectable medications. The use of depots should go a long way towards reducing rates of relapse and re-hospitalization, thereby reducing personal suffering, family burden and societal costs. Literature reviews do not suggest that there is greater risk of adverse effects with depot drugs in comparison with oral medication. Fortunately the so called atypical antipsychotics have also come with depot form, thereby changing the picture of long-term management of psychosis.

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