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Resurgence of Penfluridol: Merits and Demerits

Ranjan Bhattacharyya[1]*, Rajarshi Bhadra[2], Utpal Roy[3], Sumita Bhattacharyya[4], Jayanta Pal[3], Siddhartha Shankar Saha[5]

1. MD, DNB, PhD trainee, Asst Professor & HOD, Dept of Psychiatry, Murshidabad Medical College and Hospital, Berhampore, West Bengal, India.

2. MD. Asst Professor, Dept of Pharmacology, Icare Institute of Medical Science & Research & Dr Bidhan Ch Roy Hospital, Haldia, West Bengal, India.

3. MD. Asst Professor, Dept of Anesthesiology, Murshidabad Medical College & Hospital, Berhampore, West Bengal, India.

4. DDVL, Senior Resident, Dept of Dermatology, Institute of Post Graduate Medical Education and Research, Kolkata, India.

5. MD. Senior Resident, Dept of Psychiatry, Murshidabad Medical College & Hospital, Berhampore, West Bengal, India.

ABSTRACT

Penfluridol is oral long acting depot antipsychotic introduced in 1970s. The re-emergence of the molecule in the practicing field draws attention of clinicians. The systematic search and review of literature done in order to find current perspectives of use of Penfluridol. Systematic search of prospective clinical research studies has been done. Cochrane Database review of twenty-seven studies done with a total of 1024 patients revealed that penfluridol was superior to placebo in improvement in clinical global impression and reduces the need of additional antipsychotic. Indications of penfluridol include acute psychosis, chronic schizophrenia and Tourette's syndrome. The notable adverse effects include orthostatic hypotension, osteoporosis leading to fracture in elderly, extra pyramidal side effects and QT prolongations with arrhythmia. Most of the studies were done in 1970s and 1980s when the proper conduct of clinical trials were not established.

Keywords: Penfluridol oral depot, extrapyramidal symptoms, resurgence, adverse effects, Cochrane review.

*Corresponding Author Email: rankholders06@yahoo.co.in

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INTRODUCTION

First discovered at the Janssen Pharmaceutica in 1968, Penfluridol (marketed under the trade name of Semap, Acemap Micefal, Longoperidol) is a highly potent, first generation diphenylbutyl piperidine antipsychotic. Penfluridol blocks the postsynaptic dopamine receptor in the mesolimbic dopaminergic system and inhibits the release of hypothalamic and hypophyseal hormones Unlike other drugs in the group (e.g pimozide and fluspirilene), penfluridol has an extremely long elimination half-life (approximate 66 hours) and the effect of a single dose lasts for many days (3-7 days, by some estimates)[1]. Its potency, in terms of dose needed to produce comparable effects, is similar to both haloperidol and pimozide[2]. Though it is only slightly sedative often causes extrapyramidal side-effects, such as akathisia, dyskinesiae and pseudo-Parkinsonism. It is only slightly sedative, but often causes extrapyramidal side-effects, such as akathisia, dyskinesiae and pseudo-Parkinsonism.

Indication:

Penfluridol is indicated for antipsychotic treatment of chronic schizophrenia and similar psychotic disorders, it is, however, like most typical antipsychotics, being increasingly replaced by the atypical antipsychotics. Due to its extremely long-lasting effects, it is often prescribed to be taken orally as tablets only once a week (q 7 days). The once-a-week dose is usually 10–60 mg. The molecule is available in 20 mg tab. The synthesis of penfluridol represented the result of a well-planned scientific search for a highly lipophilic compound structurally related to haloperidol and pimozide. Because of its unusual lipophilicity, penfluridol distributes extensively in fatty tissues following oral administration. This depot effect produces a very slow release of drug from the tissues, and results in a very long duration of activity. When administered clinically at oral doses of 20 to 100 mg/week, penfluridol has been found to be an effective antipsychotic agent. This frequency of dosing is consistent with the pharmacokinetic behavior of the drug in man, and does not appear to result in any inappropriate accumulation of the drug in patients. Wide variations in steady-state levels and plasma elimination half-life have been observed in patient populations[4]. It has been said that Penfluridol is the first truly long-acting oral antipsychotic agent for the treatment of acute psychosis, chronic schizophrenia and Tourette's syndrome[2,5]. First synthesized in 1968, it is a white micro-crystalline tertiary amine, only slightly soluble in water and belongs to the diphenylbutyl piperidines; pimozide also belongs tothis group[6]. Penfluridol is absorbed from the gastrointestinal tract and deposited in fatty tissue from which it is slowly released, resulting in a prolonged duration of action with a half-life of 70 hours. It is primarily excreted unchanged in the

faeces; however, some hepatic metabolism and enterohepatic recycling occur. Penfluridol is characterized pharmacologically by the traditional neuroleptic properties: cataleptogenic effect, antagonism against apomorphine and amphetamine induced stereotypes and inhibition of controlled behaviour. It also has a relatively specific antidopaminergic effect via the blocking of the dopaminergic receptor membrane[7,8].

Mode of action

Penfluridol acts by blocking the postsynaptic dopamine receptor in the mesolimbic dopaminergic system and by inhibiting the release of hypothalamic and hypophyseal hormones[9].

Pharmacokinetics

This unique, long-acting, oral neuroleptic was the end result of a systematic scientific research for a highly lipophilic molecule structurally related to haloperidol and pimozide. It is orally well absorbed from the GI tract though antacids may reduce its absorption; peak plasma concentration is attained after 2 hours. Owing to its extreme lipophilic nature, penfluridol distributes extensively in fatty tissues following oral administration. The drug is very slowly released from the tissues resulting in very long half life. Penfluridol is extensively metabolized in the liver by glucorinide conjugation. Administered clinically at oral doses of 20 to 100 mg/ week (increased up to 250 mg once a week in severe or resistant conditions.), penfluridol has been found to be an effective antipsychotic agent. Inspite of once a week administration, wide variations in steady-state plasma concentrations and elimination half-life have been observed in some patient populations. However, once-weekly dosing is an important advantage for poorly compliant patients. It is well absorbed from the GI tract (oral); peak plasma concentration reaches after 2 hours. The molecule undergoes enterohepatic recycling. and excreted via urine and faeces (as N-dealkylated metabolite). Penfluridol has half-life of sixty-six (66) hours. The elimination half-life of Penfluridol is 36 hours (initial) and 120 hours (terminal). After dosing, it enters lipid reservoirs in the body, and is gradually released from these reservoirs across succeeding days. The effective half-life of the drug is therefore long; 3-7 days, by some estimates. This allows the once-weekly dosing of the drug. Once-weekly dosing is an important advantage for patients who are poorly adherent to antipsychotic medication. Penfluridol is extensively metabolized by oxidative N-dealkylation to afford, as isolated metabolites, the beta-glucuronide conjugate of the diphenylbutyric acid derivative A1 and the unconjugated basic piperidine moiety B1. It is assumed, at this time, that the pharmacological activity is attributable to the parent compound[10,11].

Drug Interaction and adverse effect profile

A plethora of drug interactions have been observed with various drugs. These include orthostatic hypotension with MAOIs; increased sedation with alcohol, hypnotics, antihistamines, opiates; exaggerated antimuscarinic adverse effects with TCAs; possible additive effects on QT interval with type 1a antiarrhythmics, TCAs, some quinolone antibiotics (e.g. moxifloxacin) as well as fatal neurotoxicity with lithium. Adverse effects of penfluridol include those characteristic of neuroleptic therapy. Thus, treated patients may experience acute dystonia, parkinsonian symptoms, and akathisia within 48 to 96 hours. Hyperprolactinaemia is likely to occur and dose-dependent. Singly, apart from the usual anticipated extra-pyramidal side effects, it can lower threshold for seizures, orthostatic hypotension, weight gain, impaired glucose tolerance, GI intolerance. The potentially fatal adverse reactions are blood dyscrasias, neuroleptic malignant syndrome; alteration of heart conduction leading to QT prolongation and life threatening arrhythmias. Anticholinergic side effects like blurring of vision, dry mouth, retention of urine, constipation, orthostatic hypotension are common. Other adverse effects include weight gain, impaired glucose tolerance, allergic skin rashes, cholestatic jaundice, delirium, agitation, anxiety, depression, euphoria; anorexia, constipation, diarrhoea; alopecia; amenorrhoea, hypoglycaemia, hyponatraemia; hypersalivation, nausea, vomiting; bronchospasm etc. There are reports that Penfluridol can increase the risk of breast cancer. The potentially fatal adverse reactions are blood dyscrasias, neuroleptic malignant syndrome; alteration of heart conduction leading to QT prolongation and life threatening arrhythmias. Special Precautions are required during pregnancy and lactation; elderly; epilepsy; pre-existing cardiac conduction problems; hypokalaemia, hypomagnesemia; hypothyroidism[12,13,14]. The notable drug Interactions include: orthostatic hypotension with MAOIs; may increase sedation with alcohol, hypnotics, antihistamines, opiates; antacids containing aluminum salts may decrease absorption; additive antimuscarinic effects with TCAs; may reduce bromocriptine's ability to reduce serum prolactin; amphetamines may increase psychosis; may inihibit antiparkinsonian effects of levodopa; may increase risk of extrapyramidal symptoms with metoclopramide; may increase phenytoin levels (phenytoin may reduce penfluridol levels); prolongation of QT interval with type 1a antiarrhythmics, TCAs, some quinolone antibiotics (e.g. moxifloxacin), may have additive hypotensive effects with trazodone; may increase levels of valproic acid. The potentially fatal drug interaction may produce neurotoxicity with lithium. There can be other interactions and one who is on Penfluridol, should avoid foods like valerian, St John's wort, kava kava, gotu kola because of increased risk of CNS depression. For Psychoses and

schizophrenia especially those who are non-compliant the adult dose is initially, 20-60 mg weekly, increased up to 250 mg once a week in severe or resistant conditions[15].

Existing Literature

Several open as well as double-blind, uncontrolled, active-controlled, and placebo-controlled, short- and long term clinical trial data are available. These trials were conducted on chronic schizophrenia patients and showed superiority of penfluridol to placebo and comparable efficacy in acute as well as maintenance treatment of chronic schizophrenia patients. However, questions can be raised regarding the quality of data acquired and its interpretation which fails to keep up with the standards of present day research. Cochrane Database review of twenty-seven studies done mostly in the 1970s with a total of 1024 patients revealed that penfluridol was superior to placebo in improvement of global state and reducing the need of additional antipsychotic. There was no significant difference between penfluridol and the other antipsychotics like chlorpromazine, fluphenazine, trifluoperazine, thioridazine, or thiothixene as far as clinical efficacy is concerned. Penfluridol also showed superiority in keeping the patients in treatment (reduced dropout rate; 16.4%vs 31.5%, respectively, p=0.04, NNT 6 .Penfluridol for schizophrenia was compared to depot preparations of other antipsychotics. The efficacy and adverse effect profile of penfluridol are similar to other typical antipsychotics; both oral and depot. Furthermore, penfluridol has been shown to be an adequate treatment option for people with schizophrenia who fail to respond to oral medication on a daily basis and do not adapt well to depot drugs. It is also an option for chronic schizophrenia patients with residual psychotic symptoms who need antipsychotic medication regularly. Another additional advantage of penfluridol is that it is a low-cost intervention. Penfluridol did not cause excess sedation and was tolerated well when compared to other anti-psychotics. The chief drawbacks of most of these studies are poor sample size and poor reporting of outcomes. Most of the studies were done in 1970s and 1980s when the guidelines for the proper conduct of clinical trials were not established [16,17,18]. In various studies primary outcomes like death, suicide, natural causes, service utilization outcomes, hospital admission, global outcomes, clinically significant response in global state as defined by each of the studies, mental state, clinically significant response in mental state as defined by each of the studies, behaviour, leaving the study early are measured. Secondary outcome variables like service utilization outcomes like days in hospital, global outcomes, average score/change in global state, mental state, average score/change in mental state, clinically significant response on negative symptoms as defined by each of the studies, average score/change in negative symptoms, relapse as defined in the study, behaviour, clinically significant response in behaviour as defined by each

of the studies, average score/change in behaviour, extrapyramidal side effects, incidence of use of antiparkinson drugs, clinically significant extrapyramidal side effects- as defined by each of the studies, average score/change in extrapyramidal side effects, other adverse effects, general and specific number of people dropping out due to adverse effects, cardiac effects, anticholinergic effects, antihistamine effects, prolactin related symptoms, social functioning, clinically significant response in social functioning as defined by each of the studies, average score/change in social functioning, economic outcomes, quality of life/satisfaction with care for either recipients of care or careers, significant change in quality of life/satisfaction as defined by each of the studies, average score/change in quality of life/satisfaction are be in measured in Cochrane metaanalysis[16,19,20].

Indications: Past and Present

In UK (NHS), the Trust Drug and Therapeutics Committee has approved penfluridol as an option to treat people with chronic schizophrenia who do not comply with oral medication on a daily basis or those who object to depot antipsychotic. However since it is an unlicensed medication, the Trust monitors use of the drug very closely[21]. Indications of penfluridol include acute psychosis, chronic schizophrenia and Tourette's syndrome[2,22,23,24].

Novel role as anti-cancer agent

A relatively newer indication of penfluridol has been explored in a study indicating its role as a novel anticancer agent. Penfluridol treatment inhibited the growth of Panc-1, BxPC-3 and AsPC-1 pancreatic cancer cells in a concentration-dependent manner, lead to apoptosis as evaluated by Annexin/FITC assay and cleavage of caspase-3 and PARP, induced ER stress as well as autophagy[25]. Another study suggested that penfluridol is not only cytotoxic to cancer cells in vitro but is able to inhibit tumor growth in vivo. It was postulated that dysregulation of cholesterol homeostasis may be involved in its anti-tumor mechanisms[26].

Teratogenicity

A multi-centric randomized controlled study to assess the safety of butyrophenones in pregnancy, ruled out any major teratogenic risk in women exposed during pregnancy (mostly in first trimester). Although there were no significant difference in the rate of congenital anomalies, there were two limb defects in the butyrophenone exposed group(one each for haloperidol and penfluridol); there was documented higher rates of elective termination of pregnancy ,preterm birth, a lower median birth weight (overall) and a lower median birth weight of full term infants[27].

Pitfalls

However a comparative efficacy analyses with atypical antipsychotics has not been done. The clinical outcome in refractory schizophrenia treated with penfluridol has not been assessed. Vital data on the use of penfluridol in special populations such as pregnant or lactating women are lacking; as are data on penfluridol overdose. The available literature on Penfluridol is based on studies done more than two decades back and as mentioned earlier, there are severe inconsistencies in their design, methodology and reporting of outcome measures. Newer studies need to be formulated for effective evaluation of penfluridol and test its clinical significance in the modern era. The study on maintenance of schizophrenia in a 52 week double-blind study, once weekly doses of penfluridol were compared with once daily doses of chlorpromazine in 56 schizophrenic patients receiving maintenance treatment on an outpatient basis. Both drugs were similar in their clinical effectiveness; no major difference in side effects[28].

Dosing

A 20 mg weekly dose of penfluridol has been found to be equivalent to 3 mg daily dose of haloperidol. Doses of more than 100 mg/day have been used in severely ill psychotic patients; (up to 160 mg/week in some cases). The drug was well tolerated even at these high doses. But it is advisable to initiate penfluridol under cover of anticholinergic drugs for atleast the first month of treatment due to the high incidence of dystonia. Therefore, if patients relapse at the popular maintenance dose of 20 mg/week, the problem may be under dosing rather than inefficacy of the drug[10,29]. Doses of up to 160 mg/week have been used in severely ill patients and doses of more than 100 mg/day have been used in acutely ill, floridly psychotic patients. Adult initial PO dose is 20-60 mg/week. In Severe or resistant cases doses upto 250 mg/week has been prescribed[30].

Positioning

Given the very low sedative potential of the drug, penfluridol is best reserved for patients who do not have activation symptoms. This may be the reason why penfluridol is chiefly used in chronic schizophrenia and during maintenance therapy.

General notes

One cause of relapse and readmission to hospital is poor compliance with antipsychotic medication often due to its adverse effects. Schizophrenia may also affect a person's insight, interfering with their ability to appreciate the benefit of taking medication long term. The relapse rate is significantly higher in those who have discontinued antipsychotic medication Penfluridol is an oral antipsychotic which is reputed to give antipsychotic protection for one week. This could prove a favourable option for treating those who do not wish to take daily or depot medication. Penfluridol has not been compared with atypical antipsychotics, nor has it been studied in refractory

schizophrenia. There are reports of increased incidence of orthopaedic fractures associated with use of Penfluridol especially in elderly. [32] There are no data on penfluridol overdose, nor useful information on its use in special populations, such as women who are pregnant or lactating. [33]

Efficacy

There is a large quantity of open and double-blind, uncontrolled, active-controlled, and placebo-controlled, and short- and long-term clinical trial data available on penfluridol. Almost all the trials were conducted on patients with schizophrenia, particularly chronic schizophrenia. The quality of the data is poor by present-day standards, but is on par with what was considered to be good research in the era in which the data were acquired. In summary, penfluridol was found to be superior to placebo in the acute as well as maintenance treatment of schizophrenia. Penfluridol was also found to be comparable with other neuroleptic treatments, including depot antipsychotics. The efficacy of penfluridol was confirmed in maintenance treatment studies that lasted up to one year. Considering the high rates of psychotic patients' non adherence to treatment, this is an important finding suggesting that Mobile Mental Health Units in rural areas may ensure regular antipsychotic drug treatment, which is the cornerstone of the management of psychotic disorders. [31]

Special Populations

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Caution should be exercised in patients with history of epilepsy, preexisting heart diseases, decrease in potassium and magnesium level in blood, deficiency of thyroid hormone, elderly, during pregnancy and breastfeeding[33].

CONCLUSION

Although there are shortcomings and gaps in the data, there appears to be enough overall consistency for different outcomes. The efficacy and adverse effects profile of penfluridol are similar to other typical antipsychotics; both oral and depot. Furthermore, penfluridol is shown to be an adequate treatment option for people with schizophrenia, especially those who do not respond to oral medication on a daily basis and do not adapt well to depot drugs. One of the results favoring penfluridol was a lower dropout rate in medium term when compared to depot medications. It is also an option for chronic sufferers of schizophrenia with residual psychotic symptoms who nevertheless need continuous use of antipsychotic medication. An additional benefit of penfluridol is that it is a low-cost intervention.

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