Protocol for the use of Unlicensed Thioridazine

Indication

Thioridazine is an unlicensed antipsychotic medicine indicated for individuals (18 and over) who received and responded to thioridazine prior to July 2005 and who have failed to respond adequately to alternative medication. Its use is associated with dose related QTc prolongation that predisposes individuals to potentially fatal Torsades de Pointes. Due to this it was withdrawn from the UK market in July 2005. This protocol is designed to cover the use of thioridazine in the remaining few patients that remain on this treatment. In the unlikely event of a further patient request for thioridazine, a full unlicensed medication request form and a comprehensive psychiatric medication review completed by an experienced mental health pharmacist would be required to be submitted to the Prescribing Management Group (Mental Health) for approval.

Informed consent

Due to its unlicensed status, informed consent and explanation for the rationale of treatment choice must be obtained prior to treatment initiation.[1] Patient information explaining unlicensed medication in general terms is available via the Choice and Medication portal.[2] Where there is a lack of capacity, adherence to the principles within the Adults with Incapacity (Scotland) Act, 2000 and/or Mental Health (Care and Treatment) (Scotland) Act 2003 is mandatory.

Documentation

The consultant psychiatrist must make a clear record of the rationale for prescribing an unlicensed medication within the patient's case notes and document the discussion regarding consent.[1]

In-patient prescribing and administration

Nursing staff in the ward must be informed of the medicine's unlicensed status by the prescriber and ward clinical pharmacists must ensure that staff are aware of the unlicensed status.

When ordering thioridazine, the patient's initials and CHI should be included on the requisition as well as the phrase "as per protocol" for the order to be processed. A record of administration of unlicensed medication must be kept (as per unlicensed medication policy).[3] This must include drug batch numbers, patient name and CHI number. The comments section of the recording sheet may be used for the purpose of documenting the batch number. It is the responsibility of the nurse in charge to ensure this occurs.

When supplying thioridazine from pharmacy, pharmacy staff must ensure that batch number is documented on the prescription or requisition.

Out-patient prescribing

Thioridazine will be supplied via the dispensary at Leverndale Hospital. GPs should not be asked to prescribe it. The consultant psychiatrist is responsible for ensuring that adequate physical health monitoring takes place (see details of monitoring requirements).

Review

Need for ongoing prescription of an unlicensed medicine should be assessed on a 6 monthly basis.

Approved by Prescribing Management Group (Mental Health)
Updated October 2017
Review date Oct 2020

Monitoring

MINIMUM MONITORING REQUIREMENTS FOR THIORIDAZINE TREATMENT [4]

	ECG	U&Es including Ca^{2+}, Mg^{2+} & K^{+}
Baseline	Yes	Yes
Before each dose increase	Yes	Yes
After a week of reaching 600mg daily	Yes	N/A
Six monthly intervals	Yes	Yes

- Gradually discontinue thioridazine over 1-2 weeks if QTc interval greater than 500msec.[5]
- Do not initiate thioridazine if baseline QTc interval is >450msec (males) and >470msec (females) [5]
- Any imbalance of Serum calcium, magnesium and potassium should be corrected if patient is to be initiated/ maintained on thioridazine

Dose range [5,6]

- Adult out-patient - up to 200mg daily (usually in divided doses)
- Adult inpatient – up to 600mg daily (usually in divided doses)
- Older adults – therapeutic dose is lower in this population therefore start lower and adjust according to response
- Adolescent – the use in adolescents is outwith this protocol.

Evidence base

Thioridazine is an effective antipsychotic but carries a high risk of causing serious adverse events.

Proposed mode of action

Thioridazine is a piperidyl substituted phenothiazine antipsychotic with antagonistic activity at D_1 and D_2 receptors.

Side effects [5,7]

Very common	(> 1 in 10)	sedation and drowsiness
Common	(<1/10 and >1/100)	dizziness, dry mouth, visual disturbance, nasal congestion, postural hypotension, galactorrhoea
Uncommon	(<1/100 and >1/1000)	confusion agitation, hallucinations, irritability, headache, nausea, vomiting, diarrhoea, constipation, lack of appetite, urinary incontinence or retention, ECG changes, tachycardia, amenorrhoea, menstrual disturbance, weight change, erectile dysfunction, abnormal ejaculation and abnormal LFTs

Rare	(<1/1000 and >1/ 10,000)	pseudoparkinsonism, convulsions, extrapyramidal symptoms, tremor, rigor, akathisia, dystonia, dyskinesia, hyperkinesia, tardive dyskinesia, pallor, tremor, cardiac arrhythmias, priapism, leucopenia, thrombocytopenia, agranulocytosis, hepatitis, dermatitis, skin rash, urticuria, photosensitivity, swelling of the parotid gland, hyperthermia, respiratory depression, retinitis pigmentosa**
Very rare	(<1/10,000)	depression, insomnia, nightmares, psychotic reactions, neuroleptic malignant syndrome*, paralytic ileus, Torsade de pointes, peripheral oedema, anaemia, leukocytosis
Not known		thromboembolism

Should a patient develop signs suggestive of neuroleptic malignant syndrome (NMS), all antipsychotics should be discontinued and immediate referral to an acute hospital is required.

**Pigmentary retinopathy has been reported during long term treatment and with high doses.

Contraindications[5]

- Hypersensitivity to thioridazine or any of the excipients
- Hypersensitivity to other phenothiazines
- Concomitant medication which prolongs QTc interval, inhibits cytochrome P450 2D6 or delays metabolism of thioridazine
- Severe heart disease particularly related to arrhythmias
- Congenital or acquired cytochrome P450 2D6 isoenzyme deficiency
- Comatose states and severe CNS depression
- History of haematological disorders
- Breastfeeding

Cautions[5]

- History of cardiovascular disease
- Risk factors known to predict for or aggravate arrhythmia – close monitoring
- Neuroleptic Malignant Syndrome (NMS) – may present with hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated creatinine kinase levels
- Low leukocyte and/or neutrophil counts or a history of bone marrow depression – perform FBC regularly for first 3-4 months of therapy
- Postural hypotension- monitor blood pressure when starting treatment
- Narrow-angle glaucoma
- Urinary retention
- Constipation
- Hepatic impairment
- History of seizures
- When discontinuing thioridazine do so over a period of 1-2 weeks to avoid withdrawal symptoms

Interactions[5]

Concomitant medication	Potential interaction
CYP 2D6 inhibitors e.g. fluoxetine, paroxetine, fluvoxamine, pindolol, propranolol, moclobemide, sertraline* (weak, dose-related, moderate at 150mg daily)	May considerably delay the metabolism of thioridazine. The resulting elevations in thioridazine levels increase the risk of QTc prolongation and cardiac arrhythmias. (see contraindications)
Medications which prolong QTc interval	Increased risk of QTc prolongation and potentially fatal cardiac arrhythmias (see contraindications)
Tricyclic antidepressants	May result in increased plasma levels of either or both
Phenytoin	Can increase or decrease plasma levels of phenytoin
Barbiturates	Can reduce serum concentrations of both drugs
Anticoagulants	May decrease prothrombin time
CNS depressants e.g. alcohol, benzodiazepines, anaesthetics	Effects can be potentiated
MAOIs	Can prolong sedative and anticholinergic effect
Lithium	Potential neurotoxic complications
Anticholinergic medication	Exacerbate anticholinergic effects
Levodopa	Reduced efficacy of both
Adrenergic vasoconstrictors e.g. ephedrine, phenylephrine	Reduction in hypertensive effect
Quinidine	Myocardial depression
Antiarrythmic agents	May induce ECG changes
Thiazide diuretics	Severe hypotension
Antidiabetics	Interferes with carbohydrate metabolism
Antacids	May reduce absorption of thioridazine

*Sertraline- weak CYP 2D6 inhibitors, dose-related, moderate at 150mg daily[8]

References

1. GMC Good practice in prescribing and managing medicines and devices. Updated Dec14 http://www.gmc-uk.org/guidance/ethical_guidance/14316.asp
2. Choice and Medication. Unlicensed medications handy fact sheet and olanzapine PIL http://www.choiceandmedication.org/nhs24/
3. NHS Greater Glasgow and Clyde Area Drug and Therapeutics Committee Policies Relating to the Management of Medicines Section 9.1 Acute Unlicensed Medicines Policy (ULM Policy)
4. NHS Lothian. Shared Care Agreement. Thioridazine for the treatment of schizophrenia in adults. April 2016
5. Summary of Product Characteristics Thioridazin-neuraxpharm. Nov 2012 (obtained via IDIS)

6. Martindale. The Complete Drug Reference. https://www.medicinescomplete.com/mc/martindale/2009/ Accessed 8/8/17
7. Patient Information Leaflet. Thioridazin-neuraxpharm. Aug 2015
8. Bazire S. Psychotropic Drug Directory 2016; Lloyd Reinhold Publications