PRODUCT MONOGRAPH

[Pr]pms-PIMOZIDE

(Pimozide Tablets USP)

2 and 4 and 10 mg

Antipsychotic Agent

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THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTION AND CLINICAL PHARMACOLOGY

Pimozide is a diphenylbutylpiperidine derivative with neuroleptic properties that has been found to be useful in the management of chronic schizophrenic patients. It is relatively non-sedating and can be administered in a single daily dosage.

It is assumed that the basic mechanism of action of pimozide is related to its action on central aminergic receptors. It appears to have a selective ability to block central dopaminergic receptors, although it affects noradrenaline turnover at higher doses. The extrapyramidal effects typical of other neuroleptic agents are seen also with pimozide, but it appears to have fewer autonomic effects. As with other neuroleptics, endocrine effects and ECG changes have also been reported with pimozide.

Pharmacokinetics

More than 50% of a dose of pimozide is absorbed after oral administration. Peak serum levels occur generally six to eight hours (range: 4-12 hours) after dosing. Pimozide appears to undergo

significant first-pass metabolism. Pimozide is extensively metabolized, primarily by N-dealkylation in the liver. Two major metabolites have been identified: 1-(4-piperidyl)-2-benzimidazolinone ana 4,4-bis(4-fluorphenyl)butyric acid. These metabolites have no antipsychotic activity. Only a very small fraction of pimozide is excreted unchanged in the urine. The major route of elimination of the metabolites is through the kidney.

The mean elimination half-life of pimozide in schizophrenic patients was approximately 55 hours. There was a more than ten-fold interindividual difference in the area under the serum pimozide level time curve and an equivalent degree of variation in peak serum levels among patients studied. The significance of this is unclear, since there are few correlations between plasma levels and clinical findings.

INDICATIONS AND CLINICAL USE

pms-PIMOZIDE is indicated in the management of the manifestations of chronic schizophrenia in which the main manifestations do not include excitement, agitation or hyperactivity. Pimozide has relatively little sedative action and can be used as a once-daily medication.

Pimozide is not indicated in the management of patients with mania or acute schizophrenia.

CONTRAINDICATIONS

Pimozide is contraindicated in central nervous system depression, comatose states, liver disorders, renal insufficiency, and blood dyscrasias, and in individuals who have previously displayed hypersensitivity to the drug. It should not be used in depressive disorders or Parkinson's syndrome.

Pimozide therapy is contraindicated in patients with congenital long QT syndrome or with a family history of this syndrome and in patients with a history of cardiac arrhythmias or Torsade de Pointes.

A pre-treatment ECG is thus recommended to exclude these conditions.

Pimozide should not be used in the case of acquired long QT interval, such as associated with concomitant use of drugs known to prolong the QT interval (see DRUG INTERACTIONS), known hypokalemia or hypomagnesemia, or clinically signficant bradycardia.

The concomitant use of CYP 3A4-inhibiting drugs such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone is contraindicated. The concomitant use of CYP 2D6-inhibiting drugs such as quinidine is also contraindicated. The inhibition of either or both cytochrome P450 systems may result in the elevation of pimozide blood concentration and increase the possibility of QT-prolongation.

Pimozide is contraindicated with concomitant use of serotonin reuptake inhibitors, such as, sertraline, paroxetine, citalopram and escitalopram (see DRUG INTERACTIONS).

WARNINGS

Increased Psychomotor Activity

Clinical trials with pimozide indicate that it is not effective in, and therefore should not be used in the management of manifestations of chronic schizophrenia in which the main symptoms include agitation, excitement and anxiety.

Cardiovascular

There have been very rare reports of QT prolongation, ventricular arrhythmias, and Torsade de Pointes in patients without risk factors for QT prolongation administered therapeutic doses of pimozide, and in the setting of overdose. Ventricular tachycardia and ventricular fibrillation (in some cases with fatal outcomes) have also been reported, in addition to very rare reports of sudden death and cardiac arrest.

As with other neuroleptics, cases of sudden, unexpected deaths have reported with pimozide at recommended doses and in the setting of overdoses.

Many drugs that cause QT/QTc prolongation are suspected to increase the risk of Torsade de Pointes. Generally, the risk of Torsade de Pointes increases with the magnitude of QT/QTc prolongation produced bu the drug. Torsade de Pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

An ECG should be performed prior to initiation of treatment with pimozide, as well as periodically during treatment (although there is no proof that periodic ECG monitoring will reduce the risk of Torsade de Pointes). If repolarization changes (prolongation of QT interval, T-wave changes or U-wave development) appear or arrhythmias develop, the need for treatment with pimozide in these patients should be reviewed. They should be closely monitored and their dose of pimozide should be reduced or the drug discontinued. If QT or QTc exceeds 500 msec, pimozide should be discontinued.

Particular care should be exercised when administering pms-PIMOZIDE (pimozide), or its use avoided in patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QT/QTc-prolonging drug. Risk factors for torsade de pointes in the general population include, but are not limited to, the following:

• female
• age 65 years or older
• baseline prolongation of the QT/QTc interval
• presence of genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes
• family history of of QT prolongation,or sudden cardiac death at <50 years
• cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease)

• history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation)
• electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
• bradycardia (<50 beats per minute)
• acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma)
• nutritional deficits (e.g., eating disorders, extreme diets)
• diabetes mellitus
• autonomic neuropathy
• hepatic dysfunction, renal dysfunction, and/or phenotypic/genotypic poor metabolizers of drug metabolizing enzyme isoforms, if relevant to the elimination of the drug.

Physicians who prescribe drugs that prolong the QT/QTc interval should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug..

Hypotension may very rare occur.

Liver Disease

Caution is advised in patients with liver disease because pimozide is metabolized in the liver.

Tardive Dyskinesia

As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or after drug discontinuation. The syndrome is mainly characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dosage is increased or when a switch is made to a different antipsychotic drug. Treatment should be discontinued as soon as possible.

Neuroleptic Malignant Syndrome

In common with other antipsychotic drugs, pimozide has been associated with neuroleptic malignant syndrome: an idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment should be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Withdrawal Emergent Neurological Signs

Generally, patients receiving short-term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described above under 'Tardive Dyskinesia' except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but, until further evidence becomes available, it seems reasonable to gradually withdraw use of antipsychotic drugs.

In schizophrenia, the response to antipsychotic drug treatment may be delayed. If drugs are withdrawn, recurrence of symptoms may not become apparent for several weeks or months. Acute withdrawal symptoms, including nausea, vomiting, transient dyskinetic signs, and insomnia, have very rarely been described after abrupt cessation of high doses of antipsychotic drugs. Gradual withdrawal is advisable.

Potential for Hypotension

Patients receiving pimozide should be observed for evidence of hypotension. Some individuals, especially the elderly or debilitated, have demonstrated transient hypotension for several hours following drug administration.

Seizures

As with other antipsychotic drugs, pimozide should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. In addition, grand mal convulsions have been reported in association with pimozide.

PRECAUTION

Extrapyramidal symptoms

In common with all neuroleptics, extrapyramidal symptoms may occur (see ADVERSE REACTIONS).

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing pimozide to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity or being subject to dehydration.

Endocrine Effects

Hormonal effects of antipsychotic neuroleptic drugs include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia, oligomenorrhoea or amenorrhoea, and erectile dysfunction.

Blood Dyscrasia

Leukopenia, granulocytopenia, agranulocytosis and anemia have been reported occasionally following antipsychotic therapy, notably with phenothiazines. Therefore, the possibility of blood dyscrasias cannot be ruled out in patients receiving treatment with pms-PIMOZIDE (pimozide), and they should be observed for any signs or symptoms of blood dyscrasia.

Anticonvulsants

Since pimozide may lower the convulsive threshold, it should be used with caution in epileptic patients and adequate anticonvulsive medication should be maintained.

Antiemetic Effects

As with other antipsychotics, pimozide has a substantial antiemetic effect. Thus, caution should be exercised in cases where the suppression of nausea and vomiting might hinder the diagnosis of an underlying physical disorder.

Pregnancy and Lactation

The safety of use of pimozide in pregnancy has not been established. Therefore, it should not be administered to women of child-bearing potential, particularly during the first trimester of pregnancy, unless, in the opinion of the physician, the expected benefits of the drug to the patient outweigh the potential risk to the fetus or child.

Pimozide may be excreted in breast milk. If the use of pms-PIMOZIDE tablets is considered essential, breast feeding should be discontinued.

Animal data has shown some embryo-toxicity at dose level similar to the maximum human use level (MHUL). Fetal growth retardation and fetal-toxicity was observed at dose levels of approximately 6 times the MHUL on an mg/kg basis. Teratogenic effects have not been observed.

Use in Children

Safety and effectiveness in children have not been established; therefore, this drug is not recommended for use in the pediatric age group.

Elderly

For recommendations for use in elderly see DOSAGE AND ADMINISTRATION.

Effects on Driving Ability and Use of Machinery

Pimozide may impair alertness, especially at the start of treatment. These effects may be potentiated by alcohol. Patients should be warned of the risks of sedation and advised not to drive or operate machinery during treatment until their susceptibility is known.

DRUG INTERACTIONS

CNS

Potentiation of the effects of drugs acting on the central nervous system (anesthetics, opiates, alcohol, etc.) as well as atropine and organophosphorous insecticides may occur with the use of pimozide. Both animal and human data indicate that pimozide may block the action of amphetamines. Therefore, concomitant use of the two medications is not recommended.

Levodopa

Pimozide may, in a dose-related way, impair the antiparkinson effect of levodopa.

Antihypertensives

Concomitant administration of antihypertensive agents should be undertaken with caution in view of the fact that other antipsychotics, notably the phenothiazines, have blocked the action of these agents.

Drugs that Inhibit Cytochrome P450

Pimozide is metabolized mainly via the cytochrome P450 subtype 3A4 (CYP 3A4) enzyme system and more discreetly via the CYP 2D6 subtype. In vitro data indicate that especially potent inhibitors

of CYP 3A4 enzyme system, such as azole antimycotics, antiviral protease inhibitors, macrolide antibiotics and nefazodone will inhibit the metabolism of pimozide, resulting in markedly elevated plasma levels of pimozide. In vitro data also indicate that quinidine diminishes the CYP 2D6 dependent metabolism of pimozide. Elevated pimozide levels may enhance the risk of QT prolongation.

As CYP 1A2 may also contribute to the metabolism of Pimozide tablets, prescribers should be aware of the theoretical potential for drug interactions with inhibitors of this enzymatic system.

Drugs that Prolong QT Interval

Concomitant use of pimozide with drugs known to prolong the QT interval are contraindicated (see CONTRAINDICATIONS).

Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol)
- antidepressants (e.g., fluoxetine, venlafaxine,tricyclic/tetracyclic antidepressants
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin,clarithromycin, telithromycin)
- quinolone antibiotics (e.g., moxifloxacin, gatifloxacin)
- pentamidine
- antimalarials (e.g., quinine)
- azole antifungals (e.g., ketoconazole, fluconazole,voriconazole)

• domperidone
• 5-HT3 antagonists (e.g., dolasetron, ondansetron)
• tacrolimus
• beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Particular care should be taken to avoid toxic plasma levels of lithium when this agent is administered together with pimozide, since such toxic levels have also been associated with QT prolongation.

Do not administer in combination with drugs causing electrolyte alteration. Concomitant use with diuretics should be avoided, in particular those causing hypokalemia. Other drugs that can disrupt electrolyte levels, include, but are not limited to, the following:

• laxatives and enemas
• amphotericin B
• high dose corticosteroids

Grapefruit Juice
As grapefruit juice is known to inhibit the metabolism of CYP 3A4 metabolized drugs, concomitant use of grapefruit juice with pimozide tablets should be avoided.

An in vivo study of pimozide added to steady state sertraline revealed a 40% increase in the pimozide AUC and C_{max} (see CONTRAINDICATIONS).

An in vivo study of co-administered pimozide and citalopram resulted in a mean increase of Qtc values of approximately 10 milliseconds.Citalopram did not alter the AUC and C_{max} of pimozide (see CONTRAINDICATIONS).

An in vivo study of co-administered pimozide (a single 2 mg dose) and paroxetine (60 mg daily) was associated with mean increases of 151% in pimozide AUC and 62% in pimozide C_{max} (see CONTRAINDICATIONS).

ADVERSE REACTIONS

Postmarketing Data

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with pimozide that meet threshold criteria are included in the table below. The adverse drug reactions are ranked by frequency, using the following conversion:

Very common ≥1/10

Common ≥ 1/100 and < 1/10

Uncommon ≥ 1/1,000 and < 1/100

Rare ≥ 1/1,000 and < 1/1,000

Very rare <1/10,000 including isolated repots

The frequencies provided below reflect reporting rates for adverse drug reactions (ADR) from spontaneous reports and do not represent more precise estimates that might be obtained in clinical or epidemiological studies:

Table: Adverse Drug Reactions in Postmarketing Reports

Cardiac Disorders	
Very Rare	torsade de pointes, ventricular tachycardia, ventricular fibrillation
Endocrine Disorder	
Very rare	hyperprolactinemia
Eye Disorder	
Very Rare	oculogyration
Gastrointestinal Disorders	
Very Rare	salivary hypersecretion, dry mouth, constipation
General Disorder and Administration Site Conditions	
Very Rare	hypothermia
Investigations	
Very Rare	electrocardiogram QT prolonged, electroencephalogram abnormal, blood prolaction increase

Musculoskeletal and Connective Tissue Disorders	
Very Rare	muscle rigidity, nuchal rigidity
Nervous System Disorders	
Very Rare	extrapyramidal disorder, tardive dyskinesia, bradykinesia, akathisia, dystonia, tremor, cogwheel rigidity, somnolence, headache, neuroleptic malignant syndrome, grand mal convulsion, dizziness
Psychiatric Disorder	
Very Rare	insomnia
Reproductive System and Breast Disorder	
Very Rare	galactorrhoea, amenorrhoea, gynaecomastia, erectile dysfunction
Skin and Subcutaneous Tissue Disorders	
Very Rare	rash, urticaria, pruritus, hyperhidrosis
Autonomic Effects	
	blurred vision, difficulty with accommodation, urinary retention, and urinary and fecal incontinence.
Miscellaneous	
Blood Dyscrasias	agranulocytosis, leukopenia, granulocytopenia, pancytopenia, thrombocytopenic purpura, eosinophilia, anemia, aplastic anemia

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

In general, the signs and symptoms of overdosage with pms-PIMOZIDE (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be extrapyramidal symptoms. The risk of cardiac arrhythmias, possibly associated with QT prolongation and ventricular arrhythmias including Torsade de Pointes should be considered. If these arrhythmias are severe, they can be associated with hypotension and circulatory collapse.

Treatment

There is no specific antidote to pimozide. In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary, mechanically-assisted respiration are advised. Continuous electrocardiographic monitoring should be performed due to risk of QT interval prolongation and ventricular arrhythmias including Torsade de Pointes and continued until the ECG parameters are within the normal range. Severe arrhythmias should be treated with appropriate antiarrhythmic treatment. Associated hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as dopamine or dobutamine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control centre for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

A single morning dose is recommended for all patients.

Adults

The initial recommended dose in patients with chronic schizophrenia for whom pimozide might be indicated is 2 to 4 mg once daily, with weekly increments of 2 to 4 mg until a satisfactory level of therapeutic effect is attained or excessive adverse effects occur. The average maintenance dose is 6 mg daily with the usual range of 2 to 12 mg per day. Daily doses above 20 mg are not recommended.

The patients should be reviewed regularly to ensure the minimum effective dose is being used.

Elderly patients

The maintenance dose is the same as in adults but it is recommended to start with half of the adult starting dose.

PHARMACEUTICAL INFORMATION

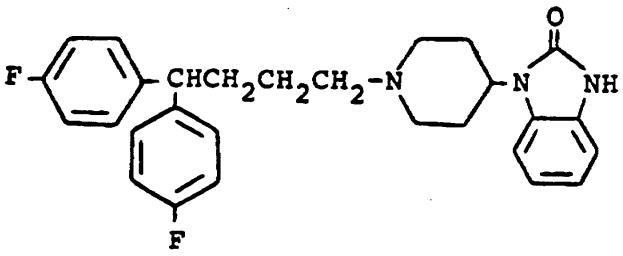
Drug Substance

Trade Name: pms-PIMOZIDE

Proper Name: Pimozide

Chemical Name: 1-{1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl}-1,3-dihydro-2H-benzimidazole-2-one

Structural Formula:



Molecular Formula: $C_{28}H_{29}F_2N_3O$

Molecular Weight: 461.56

Melting Range: 214-218°C.

Description: White to creamy-white crystalline powder.

Composition:

pms-PIMOZIDE, 2 mg Tablets contain 2 mg Pimozide USP and following non-medicinal ingredients: Calcium Stearate, Lactose, Microcrystalling Cellulose, Starch (Corn).

pms-PIMOZIDE, 4 mg Tablets contain 4 mg Pimozide USP and following non-medicinal ingredients: Calcium Stearate, Lactose, Microcrystalling Cellulose, Starch (Corn), FD&C Blue #1 Lake 13% and FD&C Yellow #5 Lake 15%.

pms-PIMOZIDE, 10 mg Tablets contain Pimozide Micronized and following non-medicinal ingredients:
Colloidal Silicon Dioxide, Croscarmellose Sodium, FD&C Yellow #6, Lactose Hydrous Spray Dried, Magnesium Stearate and Microcrystalline Cellulose.

Stability and Storage Recommendations
Store at controlled room temperature (15°C-30°C) in well-closed containers.

AVAILABILITY OF DOSAGE FORMS

pms-PIMOZIDE (pimozide) is available as tablets of the following strengths:

2 mg pimozide as white, flat face bevelled edge, uncoated tablets, scored and engraved “PIM 2" on the same side; in HDPE bottles of 100.

4 mg pimozide as green, flat face bevelled edge, uncoated tablets, scored and engraved “PIM 4 “ on the same side; in HDPE bottles of 100.

10 mg pimozide as orange, round, flat face bevelled edge tablets, scored and engraved “PIM 10" on the same side: in HPDE bottles of 100.

PHARMACOLOGY

The pharmacological profile of pimozide in laboratory animals resembles that of other antipsychotics. Its pharmacological properties are more similar to haloperidol than to chlorpromazine, but it has a slower onset and longer duration of action than either of these drugs.

As with other neuroleptics, pimozide reduces locomotor and exploratory behaviour at low doses, and induces catatonic immobility and palpebral ptosis in rats at higher doses. However, the muscle hypotonia seen regularly after administration of chlorpromazine is not observed with pimozide or haloperidol.

In inhibiting conditioned avoidance responding in rats and dogs and self-stimulation in rats, pimozide is less active than haloperidol but considerably more potent than chlorpromazine.

Pimozide is a potent antagonist to amphetamine- and apomorphine-induced stereotypy in most animal species tested. It also blocks apomorphine-induced emesis. Stereotypic chewing in rats is inhibited more than agitation by both pimozide and haloperidol, whereas chlorpromazine is significantly more active against agitation.

Pimozide has little activity in the norepinephrine test in rats. It is 66 times less active than chlorpromazine and 13 times less active than haloperidol in this test.

Typical neuroleptic catalepsy was observed in 8 out of 8 monkeys treated with 0.8 mg/kg pimozide, 6 out of 8 monkeys treated with 0.8 mg/kg haloperidol and 3 out of 8 monkeys treated with 2.5 mg/kg chlorpromazine subcutaneously. Obvious to severe extrapyramidal (dystonic) effects were observed at the same doses in 4 out of 8 pimozide-treated, 8 out of 8 haloperidol-treated and 1 out of 8 chlorpromazine-treated monkeys.

Pimozide causes no significant alterations in the hemodynamic parameters in cardiovascular experiments in rats, dogs, and dwarf pigs. It is a weak hypotensive agent and norepinephrine antagonist in rats and dogs, and exhibits very weak alpha-adrenergic blocking activity in dogs. In other tests, it has been found to antagonize the action of angiotensin on rat colon and rabbit aorta.

Bio- and histochemical studies in rats have indicated that, at the lower-dose levels, pimozide is a highly selective blocker of central dopamine receptors and increases turnover of dopamine in the central nervous system. At higher doses, increased turnover of noradrenaline has also been observed.

The following Table shows dosage details for some of the above-mentioned tests.

Comparative Activity Profiles of Pimozide, Haloperidol and Chlorpromazine

Pharmacological Test	PIM mg/kg		HAL mg/kg		CPZ mg/kg	
	S.C.	P.O.	S.C.	P.O.	S.C.	P.O.
Lowest dose producing at least 40% ptosis	2.5	2.5	1.25	1.25	2.5	10.0
Catalepsy: ED_{50}	0.2	0.22	0.12	0.22	1.32	7.07
Ptosis/Catalepsy ratio	12.5	11.0	10.0	5.0	2.0	1.3
Jumping box: ED_{50}	0.11	0.09	0.058	0.14	0.93	7.0
Sidman shock avoidance: - 50% inhibition	0.16		0.03		1.20	
Noise escape: ED_{50}	0.17		0.06		0.8	
Intracranial self-stimulation: - 50% decrease - 90% increase	 0.2 0.6		 0.08* 0.16*		 2.5* 5.0*	
Anti-apomorphine test: - lowest ED_{50} **	0.17		0.17		10.0	
Anti-amphetamine test - lowest ED_{50} **	0.11		0.032		0.63	
Anti-norepinephrine test: - lowest ED_{50} **	~40		3.1		0.6	
Anti-apomorphine test (dogs): - lowest ED_{50}	0.012	0.018	0.018	0.027	0.7	
Jumping box (dogs): ED_{50}	0.1	0.2	0.063	0.99	2.3	4.6

* Results from earlier pharmacological studies.

** The ED_{50}'s varied with time after administration; on the anti-apomorphine test the lower ED_{50} with PIM occurred at 4 hours, with HAL and CPZ at 1 hour; the respective peak values on the anti-amphetamine test occurred at 4, 1 and 2 hours and on the anti-norepinephrine test at 2, 1 and 1 hours.

Metabolism: Pimozide is well absorbed after oral administration, as demonstrated by the similarity of effective oral and parenteral doses. In rats, approximately 10% of the radioactivity of tritium-labelled doses is stored in the liver, 0.7% in blood, and 0.1% in the brain throughout the first 8 hours; thereafter the concentration in the brain decreases more slowly than that in blood and the liver. Detectable levels of radioactivity have been found in all three tissues 64 hours after the injection. In the brain, the concentration of radioactivity is highest in the caudate nucleus.

Peak levels of unchanged pimozide occur one hour after injection, whereafter they gradually decrease at a similar rate in all three tissues. The biological half-life of pimozide in rats has been estimated to be 5.6 hours. At one hour the percentage unchanged pimozide of total tritiated material was 84% in the brain, 47% in blood and 33% in the liver. The liver contained approximately 36 times more unchanged pimozide than the brain and about 11 times more than blood. When tritium-labelled pimozide was given subcutaneously to dogs, 0.13% of the dose was recovered in the brain 6 hours following the injection. Virtually all of the radioactivity present was due to unchanged pimozide. The highest concentrations were found in the pituitary gland and the caudate nucleus.

The major metabolic pathway in rats is oxydative N-dealkylation, the main metabolites being 4-bis (p-fluorophenyl) butyric acid and N-4-piperidyl-2-benzimidazolinone. It is thought that the metabolites are pharmacologically inactive, since peak pharmacological activity has been found to correlate with maximum brain levels of unchanged pimozide, but not of the total radioactivity. Most of the injected pimozide is excreted within 48 hours in rats. When 14C-labelled drug was used, 32% of the radioactivity was excreted in urine, mainly as N-4-piperidyl-2-benzimidazolinone, and 42% in the feces, half as unchanged pimozide, half as N-4-piperidyl-2-benzimidazolinone. With 3H-labelled pimozide, excretion was mainly in the feces as unchanged pimozide and as 4-bis (p-fluorophenyl) butyric acid and bis (p-fluorophenyl) acetic acid.

TOXICOLOGY

Acute Toxicity

The following table presents the results of the acute toxicity studies in rats, mice, hamsters and dogs.

Species	Sex	Route & Vehicle*	LD_{50} mg/kg (95% confidence limits)**
Rat	M	Oral(1)	> 5120
	F	Oral(2)	1430 (996-2116)
	M	S.C.(4)	> 40
	M	I.V.(4)	> 5
Mouse	M	Oral(1)	228 (141-369)
	M&F	Oral(2)	> 640
	M	S.C.(4)	> 40
	M	I.V.(4)	11.1 (7.4-16.7)
Hamster	M	Oral(2)	1100 (524-2310)
	F	Oral(2)	550 (249-1216)
Dog	M&F	Oral(3)	~ 40
	M&F	Oral(2)	> 80
	M&F	S.C.(4)	> 5

* (1) Ultrasonically micronized aqueous suspension.

(2) Suspension in Tween 80 + Syrup.

(3) Capsules.

(4) Aqueous solution with 0.1 M tartaric acid.

**Due to the poor solubility of pimozide in an aqueous medium, few actual $LD_{50's}$ could be determined; the results also varied widely with the vehicle in which the drug was administered.

When death occurred, it was frequently delayed for several days.

The main toxic symptoms noted in all species were sedation, catalepsy, and prelethal clonic seizures. In dogs, doses as low as 0.16 mg/kg p.o. or i.v. induced catalepsy and sedation, while ataxia and clonic seizures were observed at 20 mg/kg or more orally.

Subacute Toxicity

In a 14-week study, pimozide was administered in the diet in doses of 0, 0.04, 0.31 and 2.5 mg/kg/day. Sedation, decreased food consumption and reduced body weight gain were noted in the 2.5 mg/kg group only. At this dosage level, there was also a significant decrease in the absolute organ weights for almost all organs and an increase in the relative weight of the brain. No significant gross or histopathological changes were observed.

Eight dogs were given pimozide orally in gradually increasing doses from 4 to 24 mg/kg/day. Six of the animals completed 4 to 5 weeks on the drug; one male dog died on day 15 after a week on 16 mg/kg/day (ataxia and daily convulsions), and another male was removed from the study on day 16 after a week on 24 mg/kg/day, following convulsions, emesis, anorexia and a very depressed state. All animals exhibited hyperactivity, convulsions, decreased food intake, emesis and weight loss. Some hemorrhages were observed on gross pathological examination, but there were no drug-related histopathological abnormalities.

Chronic Toxicity

In an 18-month study, rats received 0, 0.025, 0.21, 1.7 and 13.3 mg/kg/day pimozide in the diet. Health, behaviour and appearance were normal in the low- and medium-dose rats throughout the study. In the two high-dose groups, sedation was noted in the first week and persisted throughout the study in the highest dose group. Decreased food consumption and body weight gain occurred also from the first week of dosing in the two high-dose groups and persisted throughout the experiment.

The only pathological change clearly related to pimozide administration was mammary activation in most medium- and high-dose females and 2 high-dose males. This response is a common feature of all potent neuroleptics, and it was observed as early as 6 months after initiation of drug

administration. Gonadal atrophy was noted terminally in a number of the males and some females. Necropsy at 18 months showed a decreased absolute weight of most organs of the animals in the two high-dose groups, while the relative weight of the brain in these groups was increased compared with controls. Significant histopathological changes were noted only in the two higher dosage groups. In the spleen there was a tendency to more hemosiderin and an increased number of lipofuscin-loaded macrophages and plasmocytes. The mesenteric lymph nodes also showed a tendency to an increased number of histiocytes in the sinuses and lipofuscin-loaded macrophages. The adrenals had minimal changes in the cortex, such as a slightly more fatty fasciculata and a few more lipofuscin-loaded cells in the reticularis in the 13.3 mg/kg dose animals. Females in both higher dosage groups had atrophic uteri and more mucified vaginas, while males had some mammary ductular development, as well as depressed secretory activity, inflammation and fibrosis of the prostate gland. Hypophyseal alterations consisted of increased numbers and signs of chronic stimulation of the erythrosinophils in both male and female rats and decreased numbers and signs of depression of the basophils in male animals. There was a greater tendency to fatty bone marrow in the highest dose animals.

In a one-year study, 40 Beagle dogs received pimozide orally 7 days a week at dose levels of 0, 0.5, 1.5 and 3 mg/kg/day. No deaths occurred at these dosages. In the treated groups, effects attributed to drug administration were mild sedation, muscular tremors, and mammary and gingival hyperplasia. Body weight loss was observed in the 3 mg/kg group only. Sedation and tremors occurred at first in most dogs, gradually decreasing in frequency and becoming rare or absent during the last nine months. Mammary hyperplasia occurred in females only and had completely regressed in all animals by the third month of the study. Lactation was observed in one high- and one medium-dose female. During the seventh month, gingival hyperplasia appeared in all high- and medium-dose dogs. The severity of the gingival hyperplasia was dose-related and the lesions persisted in all but one dog to the end of the study. There were no significant drug effects on hematology, coagulation, clinical chemistry, urinalysis, and ophthalmology. S-T and T-wave changes occurred more frequently in treated than control animals. Two animals from each group were kept for observation for 20 weeks following the termination of the one-year study. Drug withdrawal had no apparent effect on the usual clinical parameters in these dogs. However, histopathological evaluation revealed gingival hyperplasia in all mid- and high-dose animals, although only one high-dose dog showed signs of

regressed gingival hyperplasia macroscopically. Evidence of mammary hyperplasia was also observed in the mid- and high-dose females.

Carcinogenicity Studies

Mice were given pimozide as a drug/diet mixture at dosage levels of 0, 0.62, 5.0 and 40.0 mg/kg/day for 18 months. A dose-related sedative effect was noted at the 5 and 40 mg/kg dose levels.

Carcinogenicity studies revealed no treatment related tumors in rats or male mice, but increased incidences of pituitary adenomas and mammary gland adenocarcinomas in female mice.

These histopathology changes in the mammary gland and pituitary are thought to be prolactin-mediated and have been shown in rodents following hyperprolactinemia by a variety of neuroleptic drugs with the relevance to humans being questionable.

In a 24-month carcinogenicity study in rats, pimozide was mixed with the animals' normal daily diet at dosage levels of 0, 0.31, 2.5 and 20 mg/kg/day.

Clinical observations included paraphimosis in high-dose males and emaciation in mid- dose females and high-dose animals of both sexes. In addition, the testes of male rats in all drug groups were undersized and/or soft.

Reproductive Studies

In two studies pimozide was administered to female Wistar rats for the first 21 days of pregnancy: 0.16, 0.63, 2.5 and 10 mg/kg/day subcutaneously in one study and 0.04, 0.31 and 2.5 mg/kg/day by gavage in the other study. At 2.5 and 10 mg/kg s.c. and 2.5 mg/kg p.o. the food intake and weight gain of dams were decreased and their mortality rates increased. The number of pregnancies in these high-dose groups was also decreased. In the 10 mg/kg s.c. group there were no live births, all fetuses being resorbed, while in the 2.5 mg/kg s.c. group the average litter size and % live fetuses were decreased and % resorptions increased. The average birth weight of pups in both 2.5 mg/kg groups was significantly lower than in the control group, and in the orally treated group most pups showed retarded, although normal, embryological development. With the exception of the 0.63 mg/kg dams,

which showed increased resorptions and lower birth weight of pups, no adverse effects were noted in the other treated groups. Pimozide, at doses of 0.04, 0.31 and 2.5 mg/kg/day, was also administered in the diet to male rats for 60 days pre-mating and to female rats for 14 days pre-mating and throughout pregnancy. No effect was noted on male or female fertility, but the estrus cycle of dosed females was increased. No abnormalities were observed among the offspring, although the percentage of stillborn was slightly increased in the high-dose group. In a fourth rat study, 0, 0.4, 0.31 and 2.5 mg/kg/day was administered in the diet to pregnant females through days 6 to 15 of pregnancy. No significant effects were noted in any of the treated groups, although in the high-dose group the average food intake of dams was lower, the % resorptions slightly increased, and the average litter size and birth weight of pups was slightly smaller. Finally, pimozide 0, 0.04, 0.31 and 2.5 mg/kg/day was given to female rats in the diet during the last third of pregnancy and lactation. There was a decrease in the weight gain of the 2.5 mg/kg dams during the last week of pregnancy. Compared with controls, the average litter size in this group was slightly smaller, the average birth weights slightly lower, and the % of stillborn pups considerably higher. The survival rate of pups at weaning was reduced in all the treated groups in a dose-related manner.

Two studies were conducted in rabbits, pimozide being administered during days 6 to 18 of pregnancy in both. In the first study, 0, 0.16, 0.31, 0.63, 1.25 and 2.5 mg/kg/day was given by gavage to Belgian hares. There was a dose-related decrease in the percent of females found pregnant at the end of the study. No other effects were observed apart from a decrease in litter size in the 1.25 mg/kg group and a slight decrease in the birth weights in the 0.63, 1.25 and 2.5 mg/kg groups. In the second study, New Zealand white rabbits received 0, 0.16, 0.63 and 2.5 mg/kg/day pimozide, also by gavage. In the high-dose group, mortality of does was increased and the number of pregnancies slightly reduced. A dose-related decrease in the body weight gain of does was noted in all treated groups. A dose-related decrease in the average litter size was also seen in all treated groups. In the 2.5 mg/kg group, the % resorptions was increased and the % live fetuses decreased, but no other abnormalities were observed.

Mutagenicity

The results of mutagenic studies indicate no genotoxicity.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse-dominant lethal test or in the micronucleus test in rats.

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