

# FOR YOUR INPHARMATION



## PHARMACY NEWSLETTER



Volume #21, Issue #18 - December, 2001

### Sulpiride (Dogmatil®)

#### Introduction

The substituted benzamide, Sulpiride (Dogmatil®), is a selective dopamine D2 antagonist with antipsychotic and antidepressant activity. Sulpiride lacks significant activity on norepinephrine, acetylcholine, serotonin, histamine or gamma-aminobutyric acid (GABA) receptors. Structurally related to metoclopramide and trimethobenzamide, sulpiride has been used for peptic ulcer, vomiting and vertigo. Additional reports of sulpiride use in Huntington's disease, duodenal ulcer, poor lactation, contraception and treatment of tardive dyskinesia, are supported with limited data.

#### Mechanism of Action

Sulpiride is present as two optical enantiomers; (+)-sulpiride or D-sulpiride and (-)-sulpiride or L-sulpiride. The L-sulpiride is the pharmacologically active isomer.

#### Antipsychotic Activity

- Primarily a dopamine D2 antagonist, although in vitro data supports affinity for D2, D3 and D4 receptors. In addition, human PET studies demonstrate a weak affinity for D5 receptors.<sup>13</sup> At higher doses (800 to 1000 mg/day), sulpiride selectively blocks postsynaptic dopamine receptors and inhibits dopamine transmission.

#### Antidepressant Activity

- Low doses (50 to 150 mg/day) preferentially block dopamine autoreceptors, activating dopamine transmission.<sup>14</sup>
- It has been suggested that chronic treatment with low dose sulpiride induces a reduction in autoreceptor sensitivity in the A10 dopaminergic pathway.<sup>16</sup>

#### Movement Disorders

- Sulpiride appears to have a low incidence of extrapyramidal side effects (EPS). This may be due to the specific dopamine blocking activity, or to an ability to loosely bind to D2 receptors compared to dopamine.<sup>12</sup>

#### Hypoprolactinemia

- Stimulates prolactin secretion improving inadequate lactation and progestin only contraception.

#### Duodenal Ulcer

- Improves blood flow and mucus secretion.

#### Clinical Studies - Schizophrenia Studies

A 2001 Cochrane Review investigating sulpiride for schizophrenia observed that most studies were older, small and of poor quality.<sup>5</sup> Of the two hundred and twenty three citations initially identified only eighteen were included in the final review. A number of studies were excluded due to poor study design identified as a lack of/poor randomization or missing/incomplete data. Fourteen of the eighteen studies were completed in hospital setting. One study was completed in the community, but three studies did not identify the setting. The majority of the studies required a diagnosis of schizophrenia although other diagnosis were included (acute psychosis, reactive psychosis, paranoid psychosis and "syndrome dissociatif"). One small study (n=30) included two schizophrenic patients with epileptic seizures. Ten studies randomized patients with chronic illness and three with acute illness. High doses, defined as greater or equal to 800 mg/d, were used in six studies; low doses were used in another six. Only one study compared high and low doses directly. The lack of large, well-designed trials and marginal results lead the authors to conclude that there was little

difference between sulpiride and conventional antipsychotic agents. A review conducted by Mauri et. al supported the need for long term, placebo controlled studies and added the observation that data supporting the efficacy of sulpiride in negative symptoms was controversial. At low doses sulpiride had a better recovery rate for negative than positive symptoms. At high doses the recovery rate was similar for negative and positive symptoms.<sup>17</sup> In summary, sulpiride may offer a lower incidence of side effects. However, larger, long-term studies are required for further comparisons of safety or efficacy with specific symptoms or patient subgroups.

#### *Sulpiride vs Placebo*

- Three studies compared sulpiride to placebo, including a clozapine augmentation trial.<sup>11</sup> With the exception of the augmentation trial, the evidence of efficacy through improved symptoms or mental state was limited. Both sulpiride and placebo groups had similar low rates of attrition. Adverse event data was limited. These studies may be too underpowered to identify a significant difference between sulpiride and placebo.

#### *Sulpiride vs Typical Antipsychotic Drugs*

- Sulpiride has been compared to bromperidol, chlorpromazine, clozapine, haloperidol, perphenazine, timiperone, trifluoperazine and zuclopenthixol. A slight trend favouring sulpiride over typical antipsychotics was identified but statistical significance was not reached. One trial did favor sulpiride in depression (RR 0.06, CI 0.01-0.46). Patients on sulpiride had a slightly lower risk of side effects (RR 0.48, CI 0.22-1.05). There was less constipation and slightly less drowsiness and sedation (RR 0.81, CI 0.6-1.06). The incidence of movement disorders and use of antiparkinson drugs was lower for the sulpiride group (RR 0.73, CI 0.59-0.90). As a result, the sulpiride patients were less likely to leave the study early (RR 0.81 CI 0.62-1.06). Few studies reported prolactin problems. Sulpiride patients were not more likely to suffer amenorrhea compared to atypical antipsychotics but galactorrhea was

reported a significant problem (RR 1.9, CI 0.6-5.8). There was a trend for earlier studies to be more positive than later studies.

#### *Sulpiride vs Atypical Antipsychotics*

- No studies were identified that directly compared sulpiride with atypical antipsychotic agents. However, there have been reports of sulpiride augmentation of clozapine and olanzapine.<sup>8,11</sup>

#### *Sulpiride Augmentation*

- Shiloh et. al completed a 10 week double-blind placebo controlled study augmenting 28 schizophrenic patients partially responsive to clozapine with 600 mg/day of sulpiride or placebo.<sup>8</sup> Combining sulpiride and clozapine produced a clinically significant improvement in the BPRS, SAPS and SANS scores. Patients with a younger age and lower baseline SAPS scores had a mean reduction in their BPRS and SAPS scores of 42.4 and 50.4% respectively. The combination therapy was well tolerated. The major adverse event observed was a 4 to 7 fold increase in serum prolactin levels. The authors assumed that the improved antipsychotic efficacy observed with the combination was due to the enhanced dopamine blockade provided by sulpiride. Raskin et al. added sulpiride to olanzapine in 6 treatment resistant schizophrenic patients.<sup>11</sup> The average BPRS and PANSS scores for the group decreased by 25 (42.4%) and 52 (33%) respectively. No adverse effects were noted. Limitations of the study included small numbers, lack of a control group, and the open design.

#### **Antidepressant Trials**

##### *Sulpiride vs. Placebo*

- Ruther et al. completed a six week randomized, multicenter, double-blind, trial comparing 150 to 300 mg/d of sulpiride to placebo in 177 mild to moderately depressed outpatients.<sup>15</sup>

Sulpiride patients displayed a statistically significant decrease in their HAM-D scores of 2.5 points (p=0.0007). Adverse events were similar for both groups with the exception of prolactin. Fifty percent of sulpiride patients

had elevated prolactin levels. The authors concluded that sulpiride was effective and well tolerated.

#### *Sulpiride vs Amitriptyline*

- A randomized double-blind study of 36 patients with major depressive disorder compared sulpiride and amitriptyline.<sup>19</sup> Antidepressant activity was equivalent as measured by the Hamilton Rating Scale and the Wakefield Self-Rating Scale for depression.
- Thirty bipolar patients with major depression were included in a double-blind study comparing sulpiride to amitriptyline. All patients were maintained on lithium. HAM-D evaluations at 4 weeks indicated that sulpiride's antidepressant activity was equivalent to amitriptyline. Sulpiride patients experienced a faster onset of action with fewer anticholinergic effects.<sup>18</sup>

#### **Pharmacokinetics**

Bioavailability is 30% due to poor and slow gastrointestinal absorption. Administration with food also reduces sulpiride absorption by 30%. Serum levels peak in 2 to 6 hours. Larger doses are associated with a longer time to maximum serum concentration. Serum levels range from 0.05 to 0.2 mcg/ml following a 100 mg oral dosage and 0.2 to 2 mcg/ml following a 200 mg oral dosage. There is no apparent correlation between plasma levels and clinical response. Plasma protein binding is low. Sulpiride does not appear to be metabolized and drug metabolites have not been identified. Seventy to ninety percent of intravenous sulpiride is excreted unchanged in the urine. Fifteen to twenty-five percent of an oral dose is excreted unchanged in the urine. Incomplete absorption of oral sulpiride results in a significant percentage of the dose being recovered in the feces. The elimination half-life of the parent compound is 6 to 8 hours. Renal insufficiency increases the half-life of intravenous dosages to 20 to 26 hours.

#### **Adverse Effects**

The adverse effects for sulpiride are similar to other neuroleptic agents. Predominant adverse effects include extrapyramidal symptoms (EPS) and sedation (25%). Sulpiride has been associated with

tardive dyskinesia, neuroleptic malignant syndrome (NMS) and cholestatic jaundice.

- *Cardiovascular:* Palpitations, reports of worsening of hypotension.
- *CNS:* Sedation or drowsiness, dizziness, depression, sleep disturbances, headache, restlessness and impaired concentration.
- *Extrapyramidal Effects:* Parkinsonian symptoms, acute dystonias, akathisia, tardive dyskinesia and tardive dystonia.
- *Neuromuscular Effects:* One case of NMS reported.
- *Endocrine/Metabolic:* Galactorrhea, breast engorgement and galactorrhea have been reported occasionally. Menstrual disorders and amenorrhea. Sulpiride is known to induce a dose related prolactin elevation.<sup>17</sup>
- *Gastrointestinal:* Xerostomia and constipation. Nausea, vomiting, and anorexia.
- *Liver:* Hepatotoxicity, cholestatic jaundice reported in one patient.
- *Ocular:* Blurred vision.
- *Skin:* Diaphoresis.

#### **Recommended Monitoring**

Periodic liver and renal function tests. Patients should be counselled to report signs and symptoms of EPS.

#### **Cautions**

*Contraindicated;* pheochromocytoma, Parkinson's disease or patients demonstrating hypersensitivity to sulpiride. Patients with hypersensitivity to other benzamide derivatives (i.e. metoclopramide) may be sensitive to sulpiride.

*Caution;* patients with cardiovascular disease, renal insufficiency, epilepsy, hyperthyroidism, pulmonary disease or urinary retention. Sulpiride may exacerbate the symptoms in manic or hypomanic patients.

Elderly patients may have an increased risk of adverse effects. Reduced renal function may require dosage adjustments.

#### **Drug Interactions**

Administration of sulpiride with, or within 2 hours after an aluminium-magnesium hydroxide antacid

or sucralfate has been reported to significantly reduce absorption. Bioavailability is reduced 40 and 32 percent respectively. If either agent must be used concurrently, sulpiride should be given before rather than with or after antacids or sucralfate.

## Dosing Information

### Adult Dosage:

- IM: 600 to 800 mg IM daily has been used for acute schizophrenia.
- Oral: dosages of sulpiride have been reported as varying between 200 to 3200 mg/day (2 to 3 divided doses). The usual recommended oral dosage is 200 to 400 mg/day, increasing to a maximum of 1200 mg/day. Acute, untreated patients may require lower doses; chronic, severely ill schizophrenic patients may require higher dosages.
- *Dosage Adjustments in Renal Failure:*
- Reduce dose or increase dosage interval to adjust for renal function changes.

Creatinine Clearance (ml/min)	Dosage Reduction	Increase in Dosage Interval
30 – 60	70%	1.5 times
10 – 30	50%	2 times
<10	34%	3 times

## Summary

Small, poorly designed studies confound the evidence supporting the use of sulpiride in acute and chronic schizophrenia. One, well designed, placebo controlled trial augmenting clozapine with sulpiride provides evidence of efficacy. This study suggests the pharmacological specificity of sulpiride may provide an opportunity to fine tune treatment in selective cases. In addition, the lower incidence of motor side effects observed with sulpiride use may be an advantage to patients. In monotherapy, sulpiride's efficacy treating acute and chronic schizophrenia may not offer a significant advantage over traditional antipsychotic agents.

## Availability and Cost

Oral sulpiride is available in Canada as a patient specific medication through the Special Access Program. Sulpiride injection is not available in North America.

Sulpiride \$0.97 per 200 mg tablet

Written by: Debbie Thompson, Pharm. D.

Reviewed by: Sylvia Zerjav, Pharm D. & Gordon Tse, Pharm. D.

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