



Pharmacy

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Update

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Influenza Vaccination: 1999-2000

Each year, infections due to the influenza virus result in substantial morbidity and mortality worldwide. Vaccination offers appreciable protection against the influenza virus for individuals and contributes to improved overall public health.

A new trivalent vaccine is now available for the 1999-2000 influenza season. The vaccine is recommended for patients with chronic medical disorders, children with asthma, residents of long-term care facilities, and the elderly. Health-care workers and household contacts of elderly and high-risk patients are also strongly encouraged to receive the vaccine.

Protection conferred by the influenza vaccine typically begins two weeks after vaccination and may last for six months or longer. Serum antibodies in some elderly patients can diminish more rapidly to non-protective levels. Because large outbreaks in the United States usually occur between December and early March, the optimal time to receive the vaccination is between October and November. However, administration of the vaccine is appropriate anytime from September to the end of the influenza season.

The vaccine formulation is changed annually because of the antigenic variability of the influenza virus. Antigens in the current vaccine are derived from A/Sydney/5/97-like (H3N2), A/Beijing/262/95-like (H1N1), and B/Yamanashi/166/98 viruses. The latter is antigenically similar to B/Beijing/184/93, which was included in last year's formulation.

Influenza vaccine is produced from inactivated virus grown in chicken eggs. Individuals who have experienced severe hypersensitivity reactions to eggs or egg products should not receive the vaccine. An intramuscular dose of 0.5 mL of the split-virus formulation can be administered (in the deltoid) to adults and children at least three years of age. Recipients of the vaccine may experience soreness at the site of injection, fever, and malaise that may persist for one or two days.

Questions about influenza or the vaccine should be directed to the Hospital Epidemiology Service at 6-2209 or the NIH Drug Information Service at 6-2407. For questions about the vaccination schedule, contact the Occupational Medical Service at 6-4411.

Quetiapine (Seroquel®): A Brief Review

Introduction

Quetiapine fumarate is an atypical antipsychotic indicated for the treatment of psychotic disorders. Quetiapine, FDA-approved in September 1997, joins clozapine, risperidone, and olanzapine as the fourth available atypical antipsychotic. Compared to the conventional antipsychotics, the atypical agents antagonize the serotonin (5HT_{2A}) receptors to a greater extent than the dopamine (D₂) receptors. Although the definition of atypical antipsychotic varies, it is generally accepted that these agents differ from typical antipsychotics in that they are associated with less extrapyramidal symptoms (EPS) which may translate to a reduced risk of tardive dyskinesia (TD). In addition, most atypical antipsychotics are associated with less prolactin elevation and are more effective in the treatment of negative symptoms of schizophrenia compared to the typical antipsychotics. To date, clozapine is the only agent that has been shown to be superior to the typical antipsychotics in the treatment of refractory schizophrenic patients.

Description

Seroquel® (quetiapine fumarate) is marketed by Zeneca and is available as 25-, 100- and 200-mg tablets.

Indications

Quetiapine is indicated for the treatment of psychotic disorders.

Pharmacology

Quetiapine fumarate, a dibenzothiazepine derivative, is chemically unrelated to currently available atypical antipsychotics. Similar to other atypical antipsychotics, quetiapine exhibits greater 5HT_{2A} than D₂ antagonism and is most similar to clozapine in affinities for these receptors. Quetiapine possesses affinity for 5HT_{1A} and D₁ receptors, however, the significance of these affinities in the management of psychosis is not currently well understood. Quetiapine also possesses moderate affinity for alpha (α)₁ and histamine (H₁) receptors, antagonism at these receptors has been associated with side effects such as orthostatic hypotension and sedation respectively. Quetiapine has negligible affinity for muscarinic (M₁) receptors.

Pharmacokinetics

Quetiapine is rapidly absorbed, with maximal concentration achieved in 1.5 hours. The relative bioavailability of quetiapine tablets is 100 percent compared to an oral solution. Administration of quetiapine with food slightly affects its bioavailability, with C_{max} and AUC increases of 25 and 15 percent, respectively. Quetiapine is extensively distributed, having a volume of distribution of 10 L/kg. Protein binding is approximately 83 percent. Quetiapine is extensively metabolized with < 1 percent excreted as unchanged drug. The major metabolic pathways are sulf-oxidation and oxidation which yield inactive metabolites. The cytochrome P450 3A4 (CYP3A4) isoenzyme is involved in the sulfoxidation pathway yielding the major inactive sulfoxide metabolite. Linear pharmacokinetics are depicted over the clinical dose range. The terminal half-life of quetiapine is 6 hours, studies support BID or TID dosing.

Selected Clinical Studies

Quetiapine vs. Placebo

Methods: Following a single-blind placebo washout phase, 109 patients with acute exacerbation of schizophrenia were randomized to quetiapine or placebo in a multicenter, double-blind 6 week trial. Quetiapine was initiated at a dose of 25 mg TID and titrated upward until an adequate therapeutic effect was achieved (maximum dose 750 mg/day). Primary efficacy variables were the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions Scale (CGI) scores. Included in the safety assessments were AIMS examinations and monitoring of extrapyramidal side effects (EPS) with the SAS.

Results: The mean daily dose in the quetiapine group was 307 mg (range 58 – 526). Fifty-two percent of quetiapine- and 40 percent of placebo-treated patients completed the 6 week trial. Treatment failure was the predominant reason for drop-outs (61 percent of quetiapine drop-outs

and 82 percent of placebo drop-outs). Efficacy analysis was determined via Last Observation Carried Forward (LOCF). Although the BPRS scores were significantly lower at weeks 4 and 5 compared to placebo, the scores between the two groups at week 6 failed to differ (mean change BPRS = -8.1 Q vs. -2.1 placebo; p = 0.07). A similar finding was reported for differences in CGI scores.

Low-Dose Quetiapine vs. High-Dose Quetiapine vs. Placebo

Methods: Following a single-blind placebo washout phase, 280 patients with acute exacerbation of schizophrenia were randomized to low doses (LD, \leq 250 mg/day) or high dose (HD, \leq 750 mg/day) quetiapine or placebo in a multicenter, double-blind 6 week trial. Primary efficacy variables were the BPRS and CGI scores.

Results: The mean daily doses in the LD and HD quetiapine groups were 209 (range 50 – 267) and 360 (range 50 – 566) respectively. For patients completing the trial, mean daily doses were 248 and 488 respectively. Forty-three percent of LD, 50 percent of HD, and 41 percent of placebo-treated patients completed the trial. Treatment failure was the predominant reason for drop-outs (63 percent LD, 52 percent HD, and 74 percent of placebo drop-outs). Efficacy analysis was determined via LOCF. Compared to placebo, BPRS scores were significantly lower in the HD group at all timepoints beginning at 14 days; mean change in BPRS at endpoint = -8.7 Q vs. -1.0 placebo. Similar results were obtained with CGI scores. The LD group was not significantly different from placebo using either efficacy criterion.

Quetiapine vs. Haloperidol vs. Placebo

Methods: Following a single-blind placebo washout phase, 361 patients with acute exacerbation of schizophrenia were randomized to quetiapine (75, 150, 300, 600, or 750 mg/day), haloperidol 12 mg/day or placebo in a multicenter, double-blind 6 week trial. Primary efficacy variables were the BPRS and CGI scores.

Results: Forty five percent of quetiapine, 35 percent of haloperidol, and 31 percent of placebo-treated patients completed the 6 week trial. Treatment failure was the predominant reason for drop-outs (75 percent – Q75, 85 percent – Q150, 78 percent – Q300, 67 percent – Q 600, 68 percent – Q750, 50 percent haloperidol and 86 percent of placebo drop-outs). Efficacy analysis was determined via LOCF. Compared to placebo, BPRS scores were significantly lower in the haloperidol group and in all Q groups except 75 mg/day (mean change BPRS ranged from -6.3 to -8.67 Q groups > 75 mg/day vs. +1.71 placebo). Quetiapine was not significantly different from haloperidol. Similar results were obtained with CGI scores. No dose-related decreases in BPRS or CGI scores was apparent.

Currently, there are no published clinical trials evaluating the efficacy of quetiapine compared to the other available atypical antipsychotics.

Adverse Effects

General: The most frequent adverse events reported in the clinical trials were somnolence (6 to 39 percent), dry mouth (17 percent), dizziness (4 to 11 percent), constipation

(6 to 12 percent), dyspepsia (2 to 19 percent), postural hypotension (4 to 14 percent) and weight gain (>25 percent) and were dose-related. Increases in ALT were observed in 6 to 9 percent of patients, with maximal elevations of 7 to 14 times the upper limit of normal. In general, ALT concentrations peaked between 7 and 21 days and usually returned to baseline levels by the end of the trial or shortly thereafter. Few patients with elevated ALT had similar elevations in AST. Patients with ALT elevations were clinically asymptomatic. Statistically significant decreases in T3 and T4 (generally within 20 percent of lower limit of normal) in the absence of TSH elevation were reported, the clinical significance of these findings is currently unclear.

Extrapyramidal Symptoms: At baseline, extrapyramidal symptoms (EPS) were minimal and improved or did not change in the majority (~80 percent) of patients. Quetiapine was associated with low rates of EPS, approximately 4 to 8 percent (compared to 10 percent placebo and 29 percent haloperidol). Three to 9 percent of quetiapine-treated patients received anticholinergic medications for treatment of emergent EPS during the trials. For the majority of patients, Abnormal Involuntary Movement Scale (AIMS) scores did not change appreciably from baseline. However, these trials were not of sufficient duration to definitively assess the effect of quetiapine on abnormal involuntary movements (either improvement or worsening).

Prolactin Elevation: No significant increases in prolactin concentrations were noted.

Drug Interactions

Cytochrome P450 interactions. *In vitro* data suggest that quetiapine and 9 of its metabolites will have little inhibitory effect on drugs metabolized via CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19 isoenzymes.

Phenytoin: Co-administration with quetiapine increased the clearance of quetiapine by fivefold. The dose of quetiapine may need to be increased in patients receiving phenytoin or other enzyme-inducing agents (carbamazepine, rifampin, etc.).

CYP3A4 inhibitors: Quetiapine is primarily metabolized to its major metabolite via CYP3A4. Co-administration of quetiapine with CYP3A4 inhibitors (ketoconazole, erythromycin, etc.) may necessitate a dose reduction of the former.

Precautions and Contraindications

Geriatric use: The clearance of quetiapine is reduced by 40 percent in patients \geq 65 years of age compared to young patients. Specific studies evaluating efficacy and safety of quetiapine in large numbers of elderly patients have not been performed. Due to the pharmacokinetic differences and potential increased susceptibility to side effects (i.e., orthostatic hypotension), lower starting doses and a slower titration are recommended.

Pediatric use: The safety and efficacy of quetiapine in pediatric patients has not been established.

Cataracts: The development of cataracts was observed in association with chronic quetiapine treatment in dog

studies but have not been observed in other animal models. Additionally, lens changes have been observed in patients during long-term therapy, however, a causal relationship has not been established. Examination of the lens by methods which can detect cataract formation (e.g., slit lamp) is recommended at initiation of therapy and at 6 month intervals.

Pregnancy/Lactation: Pregnancy category C. Delays in skeletal ossification and reduced body weight were detected in rat and rabbit fetuses at doses much higher than those used in humans. Maternal toxicity (decreases in body weight gain and/or death) was also observed in these same animal models. In a peri/postnatal study, there were increases in fetal and pup death and decreases in mean litter weight. Quetiapine was excreted in the milk of treated animals, it is not known if quetiapine is excreted in human milk.

Dosage and Administration

The recommended starting dose for quetiapine is 25 mg BID with increases of 25 to 50 mg BID or TID on the second or third day, as tolerated, to a target dose range of 300 to 400 mg daily by the third day. Further dose adjustments, if necessary, should be made in increments of 25 to 50 mg BID. The safety of doses > 800 mg/day have not been evaluated.

Cost*

Atypical Antipsychotic	Dose	Cost Per Month
Quetiapine (Seroquel®)	400 mg/day	\$145
Olanzapine (Zyprexa®)	10 mg/day	\$149
Risperidone (Risperdal®)	6 mg/day	\$144

* Federal Supply Schedule

Conclusion

Quetiapine is the newest psychotropic agent to join the class of atypical antipsychotics which include clozapine, risperidone, and olanzapine. Quetiapine and clozapine have a relatively lower degree of affinity for 5HT_{2A} and D₂ receptors compared to risperidone and olanzapine. This relatively lower D₂ receptor affinity of quetiapine likely is responsible for the lack of significant EPS over a broad range of doses (75 to 750 mg/day). Unlike risperidone and olanzapine, quetiapine is not associated with a dose-related prolactin elevation. Clinical trials have demonstrated superior efficacy of quetiapine compared to placebo and equal efficacy compared to haloperidol in acute exacerbation of schizophrenia. The quetiapine drop-out rates due to lack of efficacy are comparable to those reported in other clinical trials. Based on published clinical trials, the most effective dose for quetiapine is not well established but is likely > 300 mg/day. Adverse effects of quetiapine include orthostatic hypotension, somnolence, transient increased ALT, and weight gain. Due to its unique pharmacological profile, quetiapine is less likely to be associated with EPS and prolactin elevation than risperidone and olanzapine. The efficacy of quetiapine in treatment-refractory schizophrenia has not been established.

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Editors' Note

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