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Psychopharmacology of olanzapine

A review

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The development of atypical antipsychotics has revolutionised the treatment of schizophrenia, as well as providing new insights into its cause. The archetypal atypical antipsychotic is clozapine, which has therapeutic advantages over traditional antipsychotics, as well as a low potential for producing extrapyramidal side-effects (EPS) (Kane *et al*, 1988). However, clozapine causes agranulocytosis in 1% of patients, and there has consequently been a search for novel atypical antipsychotics, as efficacious as clozapine, but without the need for intensive blood monitoring. There has been much discussion of the definition and characteristics of an atypical antipsychotic drug, and an operational understanding seems to have been agreed upon, that atypical drugs have therapeutic efficacy in treating schizophrenia, without producing EPS (Deutch *et al*, 1991; Kerwin, 1994).

Clozapine also challenged the traditional dopamine D_2 receptor blockade hypothesis of antipsychotic action. This suggests that therapeutic benefit correlates directly with affinity for D_2 receptors, and therefore the degree of dopamine D_2 receptor blockade. Clozapine has a low *in vitro* affinity for D_2, combined with higher affinity for 5-HT_{2a} receptors. *In vivo*, it demonstrates low striatal D_2 receptor blockade, associated with excellent clinical response (Pilowsky *et al*, 1992). It was difficult to believe that therapeutic efficacy could be achieved by low levels of D_2 blockade without producing EPS. This led to a period of reconsideration of the D_2 receptor hypothesis, and a quest for alternative receptor models for the abnormality underlying schizophrenia. This dilemma has recently been clarified, with preliminary evidence suggesting that clozapine produces greater limbic: striatal D_2 receptor blockade than do typical antipsychotics. However, it still seems difficult to account for the greater therapeutic efficacy of clozapine compared with typical antipsychotics, based on levels of D_2 receptor occupancy alone. It remains possible that atypical antipsychotics have differential action at limbic D_2 receptors. Alternatively, atypical antipsychotics may act on more than one receptor subtype to achieve their therapeutic effects. At present, high 5-HT_{2a}:D_2 affinity is also considered important in the profile of a new atypical antipsychotic drug (Kapur & Remington, 1996).

PHARMACOLOGY

The development of novel atypical antipsychotic drugs has led to the development of a series of pharmacological tests used to characterise possible drugs. Desirable properties are similar to those of clozapine: first, *in vitro* affinity for dopaminergic and serotonergic receptors, with a receptor profile otherwise minimising side-effects of the drug. *In vivo* tests in animals can also verify that the drug shows antagonism to dopaminergic and serotonergic systems, with limbic selectivity for dopaminergic antagonism. Animal behaviour tests are used to predict efficacy in treating positive and negative symptoms and the potential for producing EPS. Olanzapine demonstrates an atypical profile in its *in vitro* and *in vivo* pharmacology.

In vitro pharmacology

In vitro receptor pharmacology has established that olanzapine interacts with the key receptors which are believed to be of interest in schizophrenia. The *in vitro* receptor affinity profile for olanzapine is similar to that for clozapine, indicative of atypical antipsychotic properties. Inhibition of binding by standard radio-labelled ligands in brain tissues, or membranes from cell lines transfected with human receptors, shows olanzapine to have a broad range of receptor affinities (Bymaster *et al*, 1996*a*, 1997; Schlicker & Marr, 1996).

Dopaminergic receptors

Haloperidol has substantial selectivity (25:1) for D_2-like (D_2, D_3, D_4) as compared with D_1-like (D_1, D_5) receptors. Olanzapine (D_2/D_1 ratio of about 3:1), like clozapine (0.7:1), interacts non-selectively with all known dopamine receptors. The overall binding pattern is therefore more like that of clozapine than that of haloperidol, but the absolute affinities are greater for olanzapine than clozapine at each receptor subtype. Ratios of olanzapine:clozapine affinities are 2.7, 11.4, 5.3, 1.8 and 1.7 respectively at D_1–D_5 receptors.

Serotonergic receptors

Olanzapine has potent affinity for 5-HT_{2a}, 5-HT_{2b}, 5-HT_{2c}, and 5-HT_6 subtypes, with low affinity for 5-HT_1, 5-HT_4, and intermediate affinity for 5-HT_3 and 5-HT_7 receptors. This profile is very similar to that of clozapine at the same receptors, while haloperidol shows low affinity for all 5-HT receptors.

Muscarinic cholinergic receptors

In common with clozapine, olanzapine has high affinity for all five muscarinic receptor subtypes. In contrast, haloperidol shows low affinity for all subtypes, although some typical antipsychotics, particularly phenothiazines, have far higher muscarinic affinity. Antimuscarinic effects may contribute to the low incidence of extrapyramidal effects seen with atypical antipsychotics.

Adrenergic histaminic receptors

High affinity at these receptors contributes to the side-effect profile, rather than to the therapeutic effect. Olanzapine has an affinity intermediate between those of clozapine and haloperidol for α_1- and α_2-adrenergic receptors, which may predict fewer cardiovascular side-effects with olanzapine. All three drugs show low β-adrenergic affinity. Olanzapine and clozapine are both far more potent than haloperidol at the H_1 receptor, with all three drugs showing low affinity for H_2 and H_3 receptors.

Other

Olanzapine has a low affinity for other receptors, enzymes and key neuronal proteins, including gamma aminobutyric acid (GABA), glutamate, glycine, nicotinic, opiate and sigma receptors, ion channel

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receptors, uptake transporters, or enzymes metabolising and synthesising neurotransmitters (Bymaster *et al*, 1997).

In vivo pharmacology

Functional assays using olanzapine have demonstrated dopaminergic and serotonergic antagonism as well as dopaminergic limbic selectivity *in vivo*. Olanzapine increased the levels of the dopamine metabolite 3,4-dihydroxy-phenylacetic acid (DOPAC) in the corpus striatum and nucleus accumbens in rat brain. The increase was dose-dependent, and correlated with local D_1 and D_2 receptor occupancy, but was assumed to reflect D_2 receptor blockade, as D_1 occupancy was only 20% at a point where DOPAC was greater than half-maximal (Bymaster *et al*, 1997). Olanzapine has similarly been shown to increase homovanillic acid (HVA) levels in these brain regions (Bymaster *et al*, 1996). Evidence for *in vivo* antagonism of D_2 and 5-HT_2 receptors comes from the olanzapine blockade of increases in corticosterone induced by drugs (pergolide-D_2 and quipazine-5-HT_2). Olanzapine was over five times as potent against the 5-HT_2 than against the D_2 receptor, consistent with *in vitro* affinities (Fuller & Snoddy, 1992; Bymaster *et al*, 1997).

Further studies reflect the limbic selectivity of olanzapine, thought to be a key factor in atypical antipsychotic profile. Expression of the immediate-early gene c-*fos* is an early marker of neuronal activation. Atypical antipsychotics induce c-*fos* expression in the nucleus accumbens, consistent with efficacy in treating positive symptoms, while typical antipsychotics also increase c-*fos* in dorsolateral striatum, related to extrapyramidal effects. Clozapine also induced c-*fos* in the prefrontal cortex, thought to relate to efficacy in treating negative symptoms. Olanzapine showed a clozapine-like pattern of c-*fos* induction, reflecting its atypical properties (Deutch *et al*, 1992; Dragunow *et al*, 1992; Robertson & Fibiger, 1992, 1996; Robertson *et al*, 1994; Fink-Jensen *et al*, 1995). Electrophysiological studies show that chronic atypical antipsychotic administration reduces the number of spontaneously active dopaminergic neurons in the mesolimbic region (A10), but not the nigrostriatal region (A9). Typical antipsychotics reduce this spontaneous firing activity in both A9 and A10. Again, olanzapine showed the mesolimbic (A10) selectivity characteristic of an atypical antipsychotic (Chiodo & Bunney, 1983; White & Wang, 1983; Stockton & Rasmussen, 1996).

Behavioural pharmacology

During early drug trials, olanzapine was used in a battery of behavioural assays to predict specific receptor-mediated effects, antipsychotic potential and extrapyramidal potential. Dopaminergic antagonism *in vivo* was demonstrated by the inhibition of climbing behaviour induced in mice by dopamine agonist (apomorphine) (Moore *et al*, 1993). Olanzapine also inhibits the conditioned avoidance response, predicting high levels of antipsychotic activity. Here, rats were trained to cross their cage, on hearing a tone, to avoid shock, a response inhibited by dopamine antagonists. The dose of olanzapine required for response inhibition was then compared with the dose which induced catalepsy (a predictor of extrapyramidal symptoms), to achieve a therapeutic index for olanzapine. A ratio of 8.4 for olanzapine *versus* 2.4 for haloperidol is predictive of low extrapyramidal effects at therapeutic antipsychotic doses, and therefore an atypical profile for olanzapine (Moore *et al*, 1992). An atypical profile was also suggested by the Paw Test, in which increased hindlimb retraction latency (predicting antipsychotic activity) occurred at doses 1/20th of those increasing forelimb retraction latency (predicting extrapyramidal potential) (Cools *et al*, 1995). Further support for clozapine-like activity arose from the drug discrimination (clozapine discrimination) test in olanzapine-treated rats (Moore *et al*, 1992).

Pre-treatment with olanzapine reduces 5-HTP head twitch in mice, confirming the biochemical data on 5-HT antagonism (Moore *et al*, 1993). Olanzapine, like clozapine, reversed the effects of the non-competitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist phencyclidine (PCP) in animal studies. PCP-induced social isolation (a possible model of negative symptoms) (Corbett *et al*, 1995), hyperactivity (Gleason & Shannon, 1997), and deficits in prepulse inhibition (Bakshi & Geyer, 1995), were all reduced by olanzapine. Olanzapine has no direct affinity for the NMDA receptor. It is possible that some of these effects could be mediated by 5-HT antagonist properties of olanzapine (Maurel-Remy *et al*, 1995; Gleason & Shannon, 1997). Olanzapine showed little evidence of antimuscarinic effects *in vivo*, demonstrated by the Morris Water Maze Test in rats, in spite of high *in vitro* muscarinic affinity (Moore *et al*, 1997).

IN VIVO SCANNING STUDIES

In vivo D_2 receptor studies with ^{123}I-iodobenzamide single photon emission tomography (SPET) have shown low striatal D_2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of olanzapine and clozapine. Striatal D_2 blockade was higher in patients treated with the typical antipsychotic haloperidol, or with risperidone (Pilowsky *et al*, 1997). Low striatal D_2 occupancy by olanzapine has been substantiated in a ^{11}C-raclopride positron emission tomography study of volunteers taking a single 10 mg dose of olanzapine (Nyberg *et al*, 1997). More recently, ^{123}I-epidepride SPET studies have shown a high ratio of limbic to striatal D_2/D_2-like occupancy for clozapine (Pilowsky *et al*, 1997). This demonstrates limbic selectivity for an atypical antipsychotic *in vivo* and demonstrates that high levels of striatal D_2 occupancy are not necessary for antipsychotic effect. Research is under way to determine the pattern of occupancy for olanzapine at striatal and limbic D_2-like receptor sites. Interestingly, studies show that olanzapine shares a high 5-HT_{2a} blockade *in vivo* with clozapine (Travis *et al*, 1997).

EFFICACY OF OLANZAPINE

Early studies suggested olanzapine would be safe and efficacious in treating schizophrenia. In an early open-label trial of olanzapine (Baldwin & Montgomery, 1995), 10 patients with acute schizophrenic illness, or exacerbation of a chronic disorder, were treated with olanzapine for 4 weeks. According to scores on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), five patients responded well, two showed little change, and two deteriorated early in the study. Furthermore, minimal extrapyramidal effects were reported, and no cases of increased prolactin levels during the treatment phase.

Olanzapine was then evaluated in four double-blind controlled trials, HGAP (the US clinical trial), HGAD (the North American clinical trial), E003 (the Eastern hemisphere clinical trial), and HGAJ (the international clinical trial). Acute phase findings from each trial are documented below.

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HGAP – US clinical trial

This was a randomised double-blind placebo-controlled trial, carried out in 12 centres in the USA. One hundred and fifty-two patients meeting DMS–III–R criteria for schizophrenia were treated with olanzapine (1.0 mg/day), olanzapine 10 mg/day, or placebo, and the results of last observation carried forward (LOCF) data for mean changes in BPRS and Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987), total symptom, positive symptom and negative symptom subscales, and Clinical Global Impression-Severity (CGI-S; Guy, 1976) were compared. Scores on the BPRS and PANSS total and positive and negative symptom subscales showed a statistically significant improvement over the placebo group or all scales in the olanzapine 10 mg/day treatment group, but no improvement for the olanzapine 1 mg/day group. In this study, some patients moved from the randomised double-blind phase of the study into the open-label olanzapine trial from 3 weeks or more of treatment. Only 40% of the placebo group and 76% of the 10 mg/day group completed the entire, 6-week double-blind phase. These statistically significant improvements therefore reflected olanzapine treatment of less than 6 weeks in some cases (Beasley *et al*, 1996*a*).

HGAD – North American clinical trial

A second randomised double-blind placebo-controlled trial included 335 patients meeting DSM–III–R criteria for schizophrenia. Patients were randomly assigned to treatment with olanzapine 5 ± 2.5 mg/day, olanzapine 10 ± 2.5 mg/day, olanzapine 15 ± 2.5 mg/day, haloperidol 15 ± 5 mg/day, or placebo, for an initial 6-week phase. The trial continued with a further extended phase lasting 1 year or more. Assessment was again based on LOCF end-point analyses of BPRS, Scale for the Assessment of Negative Symptoms (SANS; Andreason, 1981) and CGI-S scores. Results for positive symptoms showed statistically significant improvement over placebo on the BPRS total and positive symptom subscales for the medium and high dose olanzapine groups and haloperidol. For negative symptoms (BPRS negative symptoms, SANS composite and summary scores), statistically significant improvement over placebo was achieved only for the high dose olanzapine group. Furthermore, the high dose olanzapine group showed statistically significant improvement over the haloperidol group in ratings on the SANS composite subscale. High dose olanzapine and haloperidol both showed statistical significance over placebo on the CGI-S rating (Beasley *et al*, 1996*a*).

E003 – Eastern hemisphere clinical trial

In a third similar study, 431 patients were treated in groups, on low, medium and high doses of olanzapine and haloperidol, with the same doses as in the HGAD trial. Here, improvements in BPRS, PANSS and CGI-S scores were compared to those achieved by a group receiving olanzapine 1 mg/day, rather than placebo. No statistically significant improvement was observed for any treatment group or primary efficacy rating over the olanzapine 1 mg/day (Beasley *et al*, 1997*a*,*c*).

HGAJ – International clinical trial

The fourth trial included 1996 patients meeting DSM–III–R criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. In a randomised double-blind active-controlled parallel study, treatment with olanzapine (5–20 mg/day) was compared with haloperidol (5–20 mg/day). Assessment of improvement in positive symptoms (BPRS total score), negative symptoms (PANSS and BPRS negative scores), global severity of illness (CGI-S), and depressive symptoms (Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979)) all showed a statistically significant superiority of olanzapine over haloperidol. Olanzapine also showed a statistically significant superiority to haloperidol in improving MADRS scores in those with severe initial depressive symptoms (Tollefson *et al*, 1997*b*).

Long-term efficacy

Patients who responded to therapy in the acute phases of trials 2–4 were able to remain in a double-blind extension phase of the trials. The maintenance effects (maintenance without hospital admission) were evaluated. For study 2, 45 patients remained an olanzapine treatment and 13 in the placebo group, for up to 1 year; 71% of the olanzapine group *versus* 30% for placebo were maintained out of hospital over this period, a statistically significant difference. In study 3, data are compared for 48 patients on the three higher doses of olanzapine, against 13 patients in the 1 mg olanzapine group. Again, inter-group differences are statistically significant, with 80% and 54%, respectively, not requiring hospitalisation over one year. Finally, extension phase data for studies 2–4 were pooled to compare olanzapine with haloperidol: 80% *versus* 72% of the olanzapine and haloperidol groups, respectively, remained out of hospital over one year, again showing the maintenance effect of olanzapine to be statistically significantly superior to that of haloperidol (Tran *et al*, 1995; Beasley *et al*, 1997*a*).

Quality of life

The Quality of Life Scale (QLS) was used in the US and International trials, over the initial 6 weeks and the extension phase periods, for a broader evaluation of clinical outcome. Differences between olanzapine and haloperidol treatment were not consistently significant. However, in the International Trial (HGAJ), statistically significant improvements in favour of olanzapine over haloperidol were seen for QLS total, intrapsychotic foundations (a measure of sense of purpose, motivation and emotional interaction) and interpersonal relations at 6 weeks. These benefits were maintained up to 1 year of treatment (Martin *et al*, 1996*a*,*b*; Revecki *et al*, 1996).

Comparison with risperidone

Olanzapine has been compared with the atypical antipsychotic risperidone in one international multicentre double-blind parallel-group 28-week prospective study of 339 patients. Both olanzapine and risperidone showed statistically significant within-treatment improvement from baseline, over 28 weeks, in PANSS total, positive symptom, negative symptom, general psychopathology, BPRS total, SANS summary and CGI scores. However, olanzapine showed significantly superior efficacy in some measures of negative symptoms, i.e. three measures of SANS summary (affect, avolition and anhedonia) scores. On PANSS total scores, a significantly greater proportion of the olanzapine group achieved 40% and 50% improvements from baseline. After 28 weeks of treatment, a significantly greater proportion of the olanzapine- than of the risperidone-treated group had maintained their improvement. Finally, the incidence of extrapyramidal side-effects, hyperprolactinaemia and sexual dysfunction were reported to be

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lower in the olanzapine-treated group (Tran *et al*, 1997*b*).

Treatment-resistant schizophrenia

While several investigators have approached this question, no clear picture is yet available. One small (n=25) uncontrolled 6-week prospective open-label study used olanzapine doses of 15–25 mg (above the manufacturers' recommended dose). Treatment resistance was defined as no response to two or more antipsychotic drugs and an initial BPRS score of 24 or greater. Thirty-six per cent of those treated showed treatment response, according to criteria of $\geqslant$35% decrease in BPRS, final BPRS $\leqslant$18, or CGI$\leqslant$3. However, only six of the 25 patients were still taking olanzapine after 6 months, which may suggest poor long-term benefit (Martin *et al*, 1997). A retrospective study suggested that olanzapine was beneficial in treatment-resistant patients, but the study did not differentiate between the treatment-resistant and intolerant groups, and used no objective symptom rating scale (Baldacchino *et al*, 1997). A further study examined the response to olanzapine at doses over the recommended 20 mg per day, for patients intolerant to clozapine (but not treatment-resistant). Findings from eight patients showed 11% improvement in total PANSS score, with none attaining the 25% improvement in PANSS which was used to define treatment response. The authors concluded that olanzapine, unlike clozapine, is not effective in treatment-resistant schizophrenia (Ratakonda *et al*, 1997).

One study reported results for four patients who had failed to respond to treatment with traditional antipsychotics, clozapine or other atypical antipsychotics, and were then treated with high-dose olanzapine (40–60 mg per day). All four patients were deemed treatment-responsive, based on Global Assessment Scale (GAS; Endicott *et al*, 1976) and CGI scores. The authors suggest that the effective dose of olanzapine may be higher than the recommended dose (Launer, 1997). A further study of eight treatment-resistant patients treated with olanzapine at 30–40 mg/day found that five of the eight suffered from extrapyramidal side-effects. All eight had prominent psychotic symptoms at the end of the trial, although social functioning had improved in four cases (Sheitman *et al*, 1997).

Summary

Olanzapine was clearly shown to be effective in treating overall psychopathology in acute schizophrenia. Olanzapine showed statistically significant or numerically superior results, compared to placebo and haloperidol, in regard to overall psychopathology. Treatment of negative symptoms and depressive symptoms in schizophrenia showed statistically significant improvement over haloperidol. As regards longer term efficacy (up to one year), there was a statistically significant reduction in relapse for the olanzapine-treated group, compared to the placebo, olanzapine 1 mg/day or haloperidol groups. A comparison with risperidone suggests that both drugs are safe and effective in treating psychotic symptoms, but the olanzapine-treated group showed greater improvement in some negative symptoms, better maintenance of therapeutic benefit, and fewer side-effects.

The benefits of olanzapine in treatment-resistant schizophrenia remain unclear, and await adequate controlled trials. At present there are no published data which compare olanzapine directly with clozapine in treatment-resistant schizophrenia.

PHARMACOKINETICS

Absorption and distribution

The pharmacokinetics of olanzapine have been studied in healthy volunteers (Boyd *et al*, 1993; Bergstrom *et al*, 1995). It is well absorbed following oral administration, with no effect from food intake. The volume of distribution (Vd) is large (10.3–18.4 l/kg), indicating that it is distributed broadly throughout the tissues. Peak plasma concentration occurs 5–8 h after oral ingestion, and is proportional to dose. Steady state is reached within 7 days of treatment. Olanzapine is 93% protein-bound in plasma.

Metabolism and elimination

Metabolism is largely hepatic, mainly conjugation, with some oxidation, mediated by cytochrome P-450 CYP1A2 and CYP2D6 isoenzymes (Kassahun *et al*, 1994; Ring *et al*, 1996*a*). *In vitro*, therapeutic doses of olanzapine have minimal inhibitory effects on other P-450 isoenzymes and therefore low potential for interaction with the metabolism of other drugs (Ring *et al*, 1996*b*).

Plasma half-life was 27–38.6 h, and median plasma clearance around 24 l/h, with excretion mainly renal. Radio-labelling an olanzapine dose, 57% was shown to be excreted in urine, and 30% in faeces. Metabolism is principally to olanzapine *N*-glucoronate, although some other inactive metabolites have been identified (Boyd *et al*, 1993). Renal insufficiency or mild to moderate hepatic impairment do not have significant effects on the pharmacokinetics of olanzapine. However, reduced plasma clearance has been shown in women (30%) and in the elderly (31%). It is recommended that a lower starting dose be considered for some patients, but the influence of these factors on pharmacokinetics was small compared to the overall variations found between subjects.

ADVERSE EFFECTS AND TOLERABILITY

Adverse effects and tolerability are central to the development of new and improved atypical antipsychotics, both in terms of the low potential for EPS, which is a defining feature of a new atypical antipsychotic, and in terms of safety and tolerability, particularly in view of the safety issues encountered with clozapine. The safety and tolerability of olanzapine were evaluated in the Phase II and III clinical trials (Beasley *et al*, 1996*a*,*b*; 1997*b*; Tollefson *et al*, 1997*b*).

Pooled data for the level of EPS in the North American, Eastern hemisphere and international trials, assessing the treatment of 1796 patients with olanzapine, are presented by Tran *et al* (1997*a*). On a variety of measures of extrapyramidal effect, they found olanzapine to be statistically significant superior to haloperidol. They also noted a significant difference in the number of patients discontinuing the study because of EPS.

Tollefson *et al* (1997*a*) present data from the same three trials on the incidence of newly emerging tardive dyskinesia in patients treated with olanzapine for a median of 237 days, and with haloperidol for a median of 203 days. They report a statistically significantly lower incidence of newly emergent tardive dyskinesia in the olanzapine group. However, long studies would be needed in order to evaluate fully the relative incidence of tardive dyskinesia in patients treated with olanzapine.

The safety profile of olanzapine has also been evaluated from these clinical

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trials. Weight gain was a common side-effect with olanzapine: mean gains of 2.2 kg and 3.5 kg are reported in the HGAP and HGAD trials, both significantly higher than with placebo. The HGAJ trial reported a mean weight gain of 1.88 kg for the olanzapine group, significantly higher than the mean gain of 0.02 kg for the haloperidol-treated group. *Post-hoc* analysis suggested that patients with low initial bone mineral index tended to be more susceptible to weight gain. Monitoring of blood pressure, body temperature and electrocardiogram showed no consistent effect of olanzapine. Postural hypotension is not believed to account for the 17% of patients who complained of dizziness. Liver enzymes showed transient elevation (alanine aminotransferase/serum glutamic-pyruvic transaminase) in 9.4% of olanzapine-treated patients. None of these patients showed signs or symptoms of hepatitis. No evidence of haemotoxicity was seen in the olanzapine-treated group, and there was no suggestion that olanzapine has any clinically significant adverse effect on bone marrow. Olanzapine did elevate serum prolactin in some patients, although not as much as haloperidol did, and this effect showed evidence of tapering off by the end of the six-week acute phase of the studies (Beasley *et al*, 1997*b*).

The most common adverse events, reported in over 10% of patients treated with olanzapine, were somnolence, asthenia, agitation, nervousness and hostility. It was suggested that these might to some extent be symptoms of the underlying illness, rather than true drug-induced symptoms; however, many appeared to be dose-dependent, suggesting that they were true drug effects. Other adverse effects reported included headache, dizziness, insomnia, constipation, anxiety and dry mouth; however, only somnolence, weight gain and constipation were statistically significantly higher than in the placebo group. Overall, olanzapine appears to be a safe drug, not very likely to produce extrapyramidal side effects or tardive dyskinesia. While a range of adverse effects were reported during clinical trials, somnolence, weight gain and constipation are the only ones reported significantly more frequently than in the placebo group.

Interactions

No interactions have been demonstrated on single dose studies with imipramine, desipramine, lithium, diazepam, warfarin or theophylline (see Lilly Industries' *Summary of Product Characteristics for Zyprexa*, 1996). *In vitro*, olanzapine showed low potential for interaction with the cytochrome enzymes involved in the metabolism of other drugs (Ring *et al*, 1996*b*). Few data are available on the effects on metabolism of olanzapine when cytochrome P-450-1A2 is inhibited by other agents. However, smoking and carbamazepine are known to induce the activity of cytochrome P-450-1A2, increasing the metabolism of olanzapine. In non-smokers, clearance was found to be 33% lower than in smokers, but the co-administration of carbamazepine increased clearance by 44%.

Contra-indications

Contra-indications include previous hypersensitivity to any ingredient of the preparation, and narrow-angle glaucoma.

Olanzapine should be used with caution for people with cardiovascular, cerebrovascular or other conditions which may predispose to the development of hypotension, for people with hepatic or renal dysfunction, and for those at risk of seizures. Caution is also advised, in view of possible anticholinergic effects, in conditions such as prostatic hypertrophy or paralytic ileus. Close monitoring is advised for patients with hepatic impairment or increased transaminases, and in patients with low leucocyte or neutrophil counts, or with a history of drug-induced bone-marrow suppression. Patients should also be monitored for tardive dyskinesia. Somnolence is a common side-effect with olanzapine, and people taking it should use caution if operating machinery or driving (see the olanzapine prescribing information, (Eli Lilly & Co.), 1996, and Lilly Industries' *Zyprexa – Summary of Product Characteristics*, 1996).

Dosage and administration

The recommended initial dose of olanzapine is 10 mg daily without regard to meals. This is a therapeutic dose. Dosage increments should be 5 mg at intervals of at least a week. Doses of 15 mg/day or more should not be given without prior clinical assessment. The tolerability of doses above 20 mg/day has not been assessed. A starting dose of 5 mg/day should be considered in people aged 65 or over and in people with renal or hepatic impairment, or who may metabolise olanzapine more slowly (non-smoking women over 65). According to the manufacturers' prescribing information, patients who respond to olanzapine should receive maintenance treatment at the lowest effective dose, and the need for treatment should be reassessed periodically.

SUMMARY

Olanzapine is a new atypical antipsychotic (Weaver, 1997). Both early development and clinical studies support its safe use. Clinical trials suggest that it is efficacious in treating positive symptoms in schizophrenia, and more efficacious for negative symptoms and depressive symptoms than traditional antipsychotics. In addition, the side-effect profile of olanzapine is favourable, with a low incidence of EPS and little increase in prolactin during acute-phase trials. At present, olanzapine appears broadly as good as the other novel atypical drugs. As a group, the atypical antipsychotics have been recommended for use as first-line therapy, in acute schizophrenic relapse, and for those who are responsive, but intolerant, to classical antipsychotic medication (Kerwin, 1994; Lieberman, 1996). The role of olanzapine in treating treatment-resistant patients is unproven, and data is awaited comparing olanzapine directly with clozapine. The current era of development of drugs for schizophrenia holds great promise, and it is the duty of all doctors to make patients aware of the benefits and risks of available treatments, and to enable them to choose.

DECLARATION OF INTEREST

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