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Atypical antipsychotic-induced blood dyscrasias and other adverse effects

Introduction

The newer generation (atypical) antipsychotics were developed with the aim of reducing extrapyramidal side effects. They are considered as efficacious as conventional antipsychotics (eg haloperidol) in reducing positive symptoms but are associated with greater improvement in negative, cognitive and depressive symptoms. Four atypical antipsychotics are currently available in New Zealand: risperidone, olanzapine and quetiapine (all first line), and clozapine (reserved for treatment-resistant schizophrenia). A summary of recent information regarding atypical antipsychotic-induced blood dyscrasias is outlined below.

Leucopenia

A minor decrease in leucocytes occurs in up to 10% of patients treated with antipsychotics (conventional and atypical). The reduction is usually small and benign and usually does not necessitate cessation of treatment.

Clozapine however is well known to cause significant leucopenia and this is not thought to be dose-related. It is estimated that 3% of patients taking clozapine have a decrease in white blood cell (WBC) count to $<3.5 \times 10^9$/L and 0.4% develop profound leucopenia (neutrophils $<0.5 \times 10^9$/L). Clozapine-induced leucopenia is most likely to occur between three weeks and three months after the first exposure, however onset after this period is also reported. The onset is usually more rapid and the leucopenia more severe if clozapine is restarted subsequently.

Pre-marketing trials of risperidone or olanzapine did not report leucopenia as an adverse effect. However, at least ten cases of risperidone-induced leucopenia have been published post-marketing. Leucopenia generally occurs within the first two weeks of treatment, but onset has been delayed (ten months in one case). Withdrawal of risperidone resulted in WBC recovery in all cases. It is currently unclear whether this is a dose-related effect.

Olanzapine has been associated with leucopenia (and isolated neutropenia) in post-marketing reports. At least twenty cases have been published in the literature, most occurring in the first four weeks of treatment although onset has also been delayed (up to thirteen months in some cases). Olanzapine withdrawal resulted in WBC recovery (assisted by granulocyte colony-stimulating factor (GCSF) in one patient).

In at least three cases, patients have been able to continue olanzapine following a dose reduction. Therefore it has been suggested that olanzapine-induced leucopenia may be a dose-related effect. In addition, one patient continued olanzapine with supplemental lithium (used to increase WBC count).

Quetiapine caused clinically significant leucopenia (not defined) in 4.2% of patients in pre-marketing trials compared to 1.9% in placebo. At least three cases of severe agranulocytosis associated with quetiapine have been published in the literature, with WBC count normalising between two days and several months after quetiapine withdrawal. There are fewer post-marketing reports linking quetiapine with severe leucopenia than with other atypical antipsychotics, possibly reflecting its later arrival on the market.

Thrombocytopenia

Thrombocytopenia induced by atypical antipsychotics-is very rare and causality is difficult to establish. Few reports have been published in the literature and product information suggests thrombocytopenia occurs in less than 0.01% patients taking clozapine and less than 0.1% of patients taking risperidone. We are only aware of two published cases associating olanzapine with reduced platelet count and one case with quetiapine.

Anaemia

Blood dyscrasias involving the red cell lineage are rarely associated with atypical antipsychotics. The incidence of anaemia was less than 1% in pre-marketing clinical trials of risperidone and is estimated as less than 0.1% in those taking clozapine. Quetiapine and olanzapine have each been linked with one case of pancytopenia, but there do not appear to be any other published reports associating these agents with anaemia.

Conclusions

Rare but serious drug-induced adverse effects are often not identified in pre-marketing studies and are only seen when a wider population has been exposed. Most atypical antipsychotic-induced blood dyscrasias are rare and many were not detected in pre-marketing trials. Atypical antipsychotics should be considered as a possible cause of blood dyscrasias if a temporal relationship exists, in which case, withdrawing the suspected agent is likely to result in WBC recovery in most situations.

A summary of other adverse effects is outlined in the table below:

		Clozapine	Olanzapine	Quetiapine	Risperidone
CNS	Seizures	++	+	+	±
	Sedation	+++	++	++	+
	Dose-dependant EPS	0	+	0	++
	Tardive dyskinesia	0	±	±	±
Metabolic/ Endocrine	Weight gain	+++	+++	++	++
	Hyperlipidaemia	+++	+++	+ to ++	± to +
	Type 2 diabetes	+++	+++	+ to ++	± to +
	Prolactin elevation	0	±	±	+++
Cardiovascular	Orthostatic hypotension	+++	+	++	++
	QTc prolongation	+	±	±	±
Other	Anticholinergic effects	+++	+	±	±

Key: 0 = absent; ± = minimal; + = mild or low risk; ++ = moderate; +++ = severe; EPS = extrapyramidal side effects