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Clozapine – A Summary

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We have been privileged to have a group of distinguished basic and clinical investigators in the neurosciences and psychiatry illustrate for us the important and perhaps unique role of clozapine in neuropharmacology and the treatment of schizophrenia. I have been invited to synthesise the various views and to set the preceding papers into context. My two qualifications for this Solomonic role are my 'neutrality', as I am not involved in research in this area, and my intense interest as a specialist whose advice is sought on the management of refractory schizophrenic patients.

We should first examine the unusual clinical properties of clozapine:

(a) effectiveness in 30–60% of otherwise treatment-resistant schizophrenics
(b) effective against negative as well as positive symptoms
(c) extrapyramidal side-effects usually mild
(d) little or no tardive dyskinesia
(e) no marked elevation of prolactin
(f) hypersalivation frequent side-effect
(g) 1–2% incidence of granulocytopenia.

The receptor binding and efficacy properties are also extensive. Thus, clozapine has antagonistic properties at dopamine, noradrenalin, serotonin (5-HT), histamine and perhaps NMDA receptors. A major immediate challenge in psychopharmacology is how to relate the plethora of pharmacological actions to the complex clinical properties of clozapine. I believe that the granulocytopenia and agranulocytosis – this unfortunate limitation on our use of clozapine – are unrelated to any therapeutic effect. In other words, it is feasible to develop safer clozapine-like compounds.

Some papers of this supplement provide updated reviews of the clinical effects of clozapine. The efficacy of clozapine, as Dr Kane outlines, is now firmly established, and attention has turned to identifying predictors of response. Because of the risks of clozapine therapy, it is important to avoid its use in patients who are unlikely to respond to it, so this approach is a very important one.

Professor Meltzer has shown that clozapine can improve several aspects of functioning but that the patterns of response differ from patient to patient. The undoubted social and economic benefits of clozapine have thrown this therapeutic topic into the political arena, which is not always to the public good.

Dr Gerlach pointed out the atypical profile of clozapine's extrapyramidal side-effects (EPS), and confirmed this using a cebus monkey model. He showed the relationships between D_1 and D_2 antagonist properties.

It behoves many of us in the USA, UK and some other countries to remember that much clinical experience has accrued in countries like Germany where clozapine has been available and used for many years. Dr Naber has shared with us his extensive experience of the practical use of clozapine. He concludes that in such real-life conditions the benefit/risk ratio for clozapine remains highly favourable. Nevertheless, as Dr Krupp was at pains to emphasise, the price of freedom to prescribe clozapine is eternal vigilance.

Other papers attempted to relate the pharmacological properties of clozapine to its clinical profile; Dr Coward provided us with a brief overview of clozapine's pharmacology.

Others concentrated on individual aspects of clozapine's action, namely, limbic selectivity (Dr Bunney), low D_1 occupancy (Dr Farde), several serotonin–dopamine interactions (Professor Meltzer) and anti-adrenergic actions (Dr Baldessarini). These hypotheses address different aspects of the clinical profile. For example, limbic selectivity is quite plausible as an explanation for low EPS and tardive dyskinesia. Low D_2 binding may also explain the paucity of EPS. The explanation for useful effects on negative symptoms may relate to the 5-HT/DA ratio. However, we need more physiological studies to establish the relevance of these binding characteristics.

We are left with the fundamental question – why the superior efficacy? Until recently, no property sufficiently differentiated clozapine from other antipsychotics. But we must not be discouraged. Our knowledge of CNS pharmacology is still rudimentary, despite the enormous advances made within our professional lifetimes. Molecular biology has now taken up the challenge and its findings are proving very relevant to our topic. As we have heard, new receptors are being described, based on cloning

techniques. The Toronto/Portland group have described a human D_4 receptor with a high affinity for clozapine (van Tol *et al*, 1991). Indeed the ratio of D_2/D_4 binding does seem to differentiate clozapine (and octoclothepin). In contrast, D_5 receptors seem irrelevant to the action of clozapine (Sunahara *et al*, 1991). This is a highly technical approach – indeed the only parts of the papers I could really understand were the titles and the acknowledgements! But, to the embattled clinician, the amino acid sequencing of the various dopamine receptors suggests that ingenious synthetic chemists will be able to develop more selective compounds which can be tested clinically. It may well be that a specific profile of effects is relevant, but before we settle for that explanation, we should explore the properties of highly monoselective compounds.

Schizophrenia remains one of the most distressing of human disorders. Clozapine has given us hope that our therapeutic efforts will be steadily more successful. And the commitment of Sandoz and other pharmaceutical companies to antipsychotic drug development programmes encourages us for the future.

References

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