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Discussion

Atypical clinical features of clozapine

Question: At what level of eosinophilia should clozapine be discontinued?

Krupp: This is a difficult problem to which haematologists appear to have no answer. Eosinophilia may occur in isolation, without associated clinical problems. We made the arbitrary decision that if the absolute count of eosinophils is higher than 1500 use of clozapine should be reduced or discontinued. Treatment may be resumed if the count returns to normal.

Hippius: If eosinophilia occurs without any other changes in white blood cells or dermatological symptoms, continued treatment with clozapine is justified. However, if eosinophilia occurs with dermatological symptoms or fever, or with a large increase in leucocytes, or with leucopenia, treatment should be stopped. The experience with eosinophilia in clozapine treatment can be compared to that with chlorpromazine in the early 1950s when similar observations were made, but the reasons for it are unknown.

Krupp: I have also been asked about the relationship between the daily dose of clozapine and occurrence of agranulocytosis. In the US trials, when doses of about 600 mg were used, there was an incidence of agranulocytosis of about 1%. After one year it was about 2%. In Finland the incidence was about 0.7% and lower doses were used (Krupp & Barnes, 1989). Using multivariate analysis we could not find a dose-related occurrence of clozapine-induced agranulocytosis (Farina *et al*, 1978). Thus at present there is no good evidence that a high dose constitutes a higher risk, but that cannot be completely excluded.

Meltzer: One reason why clozapine continued to be used after the high incidence of agranulocytosis in Finland was that in a number of European countries where clozapine was withdrawn, patients relapsed and could not be reconstituted with standard neuroleptics. We have discontinued clozapine because of agranulocytosis in four patients. One, who had improved markedly on clozapine, had a severe relapse that began 2–3 weeks after withdrawal. For over six months we have been unable to restore him to his best pre-morbid level.

Kane: We had similar experience with a group of patients transferred to our care with the recommendation that they be withdrawn from clozapine in case it became unavailable because of legal restrictions. Of the first three patients, one made a serious suicide attempt and the others had severe psychotic relapses that did not respond to other medication. We resumed clozapine treatment for all three patients and were hesitant about withdrawing any further patients.

Hippius: European clinicians continued to use clozapine after the high incidence of agranulocytosis in Finland because there was no difference between the risk of agranulocytosis with the older tricyclic neuroleptics, for example chlorpromazine, and with clozapine. Our experience in the 1950s and 1960s was that all tricyclic neuroleptics given in daily doses of more than 100 mg had the same risk, with the exception of the high incidence with clozapine in Finland. We are astonished that a risk of up to 2% is now reported in the USA. In the past ten years we have seen a decreasing risk. Continued research is necessary and I hope that the aetiology of agranulocytosis will be solved so that we have prognostic indicators to exclude patients at high risk.

Krupp: We are trying hard to do that, which is why we were interested in the data about the high risk among Ashkenazy Jews (Lieberman *et al*, 1990). Unfortunately those results have not been reproduced in European patients. We are convening a panel of experts to evaluate all possible mechanisms of drug-induced agranulocytosis. Dr Lieberman and co-workers have reported results that suggest an immunological mechanism and have identified an antibody, the relevance of which is, however, unclear (Lieberman *et al*, 1988). This is a complicated field: agranulocytosis occurs with many kinds of drugs and in most cases the aetiology is unknown. It is difficult to research events that are, fortunately, rather infrequent.

Question: What are the implications of Dr Kane's findings of a high incidence of therapy-resistance among relatively young patients, of disease duration of only seven years?

Kane: I should emphasise the difficulty in defining lack of response to treatment; the proportion of patients that are unresponsive depends on the criteria used for refractoriness. We looked for the relative absence of positive symptoms. Many patients, even in their first episode, take months to recover. We have seen that it takes a median of 11 weeks to see full improvement, even in first episode patients. We should be careful to define whether we are looking for

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a complete absence of psychopathology or a very good response that may leave some patients with residual symptoms. In our study we used the latter criterion.

Question: Why are most schizophrenics not prescribed clozapine?

Meltzer: At present, clozapine is not intended as a first-line drug in schizophrenia. It is aimed at treatment-resistant patients. Therapy resistance is a nebulous concept, as Dr Kane has pointed out, but if we apply conservative criteria, 20% of schizophrenic patients should be candidates. Perhaps 60% of those will respond, which means 12% of all schizophrenic patients will benefit. The question of the criteria for the use of clozapine falls, in my opinion, in the legitimate domain of patients, their physicians, certain family members, and perhaps society in general.

Kane: If it were not for agranulocytosis we would be using clozapine in all patients because it clearly has advantages over other treatments. Until we can reduce the risk of agranulocytosis by understanding its mechanisms we are caught in a difficult benefit-to-risk judgement.

Question: The effect of clozapine on the extrapyramidal system is complex. Some patients with marked tardive dyskinesia (TD) before clozapine treatment show no change in TD during treatment although they experience significant behavioural changes. On the other hand, a number of neuroleptic malignant syndromes have been reported during clozapine treatment in the USA. Does the first observation suggest that clozapine does not affect D_2 receptors in the nigrostriatal areas whereas the second observation seems to suggest a significant effect?

Gerlach: It is true that some patients with TD do not respond to clozapine. It is difficult to use high doses of clozapine in TD patients, who are normally elderly. Therefore we see limited effects against TD. This is probably because there is a limited D_2-blocking effect: little Parkinsonism is obtained and consequently TD is not fully suppressed. In other patients improvement may be obtained. The neuroleptic malignant syndrome is a special idiosyncratic reaction which can be induced by low blockade of D_2 receptors.

Question: Does clozapine have efficacy in resistant bipolar patients, particularly rapid cyclers or occasional chronic resistant manics?

Meltzer: With a small series of highly resistant rapid cyclers and bipolar psychotics the results have been as gratifying as with treatment-resistant schizophrenics, particularly for the suppression of manic symptoms. A few patients had breakthrough depressions after some time but the rapid cycling disappeared dramatically.

Hippius: We have treated some cases of chronic resistant depressions. The influence both on the course of the illness and on the chronic affective symptoms should be investigated.

Question: Would clozapine be expected to be better than thioxanthenes if the D_1/D_2 ratio is the key factor?

Gerlach: Clozapine has a unique D_1/D_2 blocking profile. All other drugs have very little D_1 blockade, especially in *in vivo* tests. Flupenthixol is the thioxanthene with the highest D_1-blocking effect, but compared to the D_2-blocking effect this is too low to be effective in humans.

Question: How should convulsive attacks be managed in patients on clozapine? Should the medication be changed or can an anticonvulsant be used with clozapine?

Kane: The risk of clozapine-induced seizure is dose-related and if the dose is reduced, treatment can usually be continued. If an anticonvulsant is necessary, we strongly discourage use of carbamazepine because it carries its own risk of agranulocytosis.

Question: What is the pathophysiology of the improvement in semantic memory seen with clozapine?

Meltzer: This is possibly related to clozapine's effects on the cholinergic or serotonergic (5-HT) systems. Clozapine is a potent anticholinergic agent but paradoxically causes hypersalivation, which may be related to the release of acetylcholine. It also has profound effects on the serotonin system, e.g. blockade and downregulation of 5-HT_2 receptors.

Question: How should the incidence of weight gain seen in patients treated with clozapine be viewed with respect to long-term treatment?

Naber: The incidence relates to duration of treatment. In patients treated for eight weeks we see low incidence of significant weight gain, but weight gain led to withdrawal from clozapine in 2–3% of our out-patients. In the long-term this could be a serious problem. We should try to reduce the doses, especially for out-patients. In our experience, it is usually possible to reduce the dose after six months without exacerbation of psychosis. We have some patients on a continuous dose of 25 mg and I don't think this is simply a placebo effect.

Biological hypotheses relating to the atypicality of clozapine

Question: What information about the pathophysiology of schizophrenia do the findings with clozapine give us?

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Meltzer: Attention is focused on the 5-HT/DA interaction because we have found a series of serotonergic abnormalities in schizophrenics. Compared to the difficulty of finding dopaminergic abnormalities in this disease, it is relatively easy to find such abnormalities, particularly in the 5-HT_2 system. Four of five post-mortem studies have shown downregulation of 5-HT_2 receptors in the frontal cortex of schizophrenics. When we challenge schizophrenics with MK 212, blunted cortisol, prolactin and temperature responses are observed in many patients. With *m*-chlorophenylpiperazine, which is a difficult serotonergic agonist to interpret, behavioural worsening has been seen. A Japanese group has shown abnormalities in the 5-HT_{1A} system in post-mortem studies. There is also some fascinating data from Sweden showing a 5-HT/DA imbalance.

We have also initiated a study of the response of the hypothalamo-pituitary-adrenal (HPA) axis to clozapine. Clozapine produces marked decreases in cortisol secretion, which may also be relevant to some of its unique chemical effects.

Coward: I agree that the 5-HT-blocking activity of clozapine is important, but I would like to take issue with some of Professor Meltzer's conclusions. In particular, in the analyses that have been performed, for example his multivariate binding study (Meltzer *et al*, 1989), there are false positives. For example, from the *in vitro* binding studies amoxapine should be a clozapine-like agent. Also, Professor Meltzer's group have shown that there is a consistency between clozapine and certain of the classical congeners with regard to downregulation of 5-HT_2 receptors after both chronic and acute administrations (Matsubara & Meltzer, 1989).

Meltzer: I agree that loxapine and amoxapine do not quite fit. That is one reason why we initiated *in vivo* binding studies. We found with *in vivo* binding for loxapine that dopamine receptor blockade is more potent relative to serotonergic blockade than could be anticipated from *in vitro* studies. We are following this with chronic administration. I agree that the 5-HT_2/D_2 profile is not the only factor in clozapine's action, but it still holds up that over 90% of the compounds we have studied do fit the model.

Coward: We are often asked why it is not possible to combine a selective D_2 blocker with a 5-HT_2 blocker and simply do the appropriate titration to a low dose of the D_2 blocker to give the same D_2 occupancies that Dr Farde has shown clozapine to produce and have correspondingly stronger 5-HT_2 blockade with an agent that is selective for that system.

Meltzer: We found a striking correlation between the 5-HT_2 receptor affinity and the D_2 receptor affinity for all the atypicals and for none of the other drugs. We found this with the 17 compounds in the initial paper, and it holds up with eight additional compounds. Something about these molecules with atypical properties is reacting with some subset of the D_2 receptor. The D_4 receptor could be the critical subset: the D_4/5-HT_2 relationship may be more important than the D_2/5-HT_2 relationship. The D_3 receptor does not seem to be relevant to clozapine's action.

Question: Does clozapine have a mood-elevating effect and what might the mechanism be?

Baldessarini: In the experience of my colleagues, clozapine has a clear antimanic effect. Whether this is a true mood-altering or mood-stabilising effect is hard to say. Patients who are transferred from high doses of potent neuroleptics to clozapine frequently seem brighter and more active, but it is difficult to know if this is a true elevation of mood or relief from side-effects of previous drugs.

Meltzer: Clozapine can produce mood elevation in psychotic depression. I would consider two biological mechanisms. One is downregulation of serotonin receptors, which is shared by almost all antidepressants. In particular, the combination of tricyclic antidepressants and neuroleptics downregulates the 5-HT_2 receptor. This may be the basis for their efficacy in the treatment of psychotic depression. Secondly, clozapine can enhance the release of dopamine in the midbrain area. I think that dopamine has an important effect on mood in depression. Perhaps clozapine's ability, in contrast to the typical neuroleptics, to maintain dopaminergic activity in the limbic region and to increase dopamine in the frontal cortex may contribute to its mood-elevating effect.

Question: Professor Bunney, did you consider interaction of the serotonin receptors with the dopamine system? What about other possible interactions?

Bunney: We have only looked at ritanserin so far, combining it with haloperidol to investigate whether there is some interaction that increases the chance of depolarisation block in the A9 area. We did not see it. We should try other blocking agents to see if the serotonergic system is involved. We have not looked at any anticholinergic agents other than trihexyphenidyl.

Question: Dr Farde, you showed that clozapine occupies 40–60% of the D_2 receptors. What happens if more than 600 mg is given? Does increasing the dose produce more receptor blockade and perhaps extrapyramidal side-effects (EPS)?

Farde: Based on the D_2 receptor occupancies and the doses in the patients we have examined so

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far, I estimate that the daily dose needed to produce a D_2 occupancy of 75–80%, which is the occupancy at which EPS are seen, would be more than 2000 mg. Such doses cannot be examined in patients because of safety and tolerability precautions.

Question: Which kind of EPS were seen, dystonia or Parkinsonism?

Farde: The EPS recorded in association with the positron emission tomography (PET) study were akathisia, Parkinsonism and one case of dystonia. The sample is not large enough for detailed analysis of each of these EPS in relation to receptor occupancy. Patients with Parkinsonian side-effects tend to have higher occupancies than those with akathisia.

Baldessarini: That raises an important point. We have concentrated on D_2 receptor blockade and have developed drugs over the last 40 years based on this approach. Is it possible to produce useful antipsychotic effects only by having a high proportion of disabling of the dopaminergic system? I would argue the opposite point of view, that a 'soft' or partial impact on the dopamine system with one or more of the other effects that we have discussed may be a more interesting way to go. Otherwise we shall just continue to develop drugs like the ones we know, with similar side-effects.

Question: We need the correct tools to test the hypotheses presented here. Some of these tools are emerging and are being tested in the clinic, particularly D_1 antagonists and 5-HT_2/D_2 antagonists. Do these drugs fulfil their predicted characteristics?

Farde: So far the D_1 antagonists have not been tried systematically in the clinic. We have some experience with SCH23390 in PET studies. We injected 1 mg intravenously to saturate the receptors, and we observed akathisia shortly afterwards. Thus these compounds are of functional importance in man, but we shall know more soon because more selective dopamine antagonists are being prepared for clinical studies.

Meltzer: D_1 drugs, although not D_1-selective, have been tried in the clinic. Examples are flupenthixol and zotepine, for which the D_1/D_2 ratios are comparable, at least *in vitro*, to those achieved with clozapine. I would like to see those drugs used in PET studies. I would expect the D_1 blockade to be comparable to that with clozapine. There appears to be weak D_2 blockade in the nigrostriatal region with clozapine at clinically effective doses, but our rodent evidence suggests that clozapine may achieve effective D_2 blockade in the limbic system, comparable to that obtained with typical antipsychotic drugs. The D_2 blockade is one of the cornerstones of clozapine's antipsychotic action, but some other factor, noradrenergic or serotonergic, needs to be brought into play.

Farde: According to reported *in vitro* studies, flupenthixol has equal affinity for D_1 and D_2 receptors. In PET studies it has a higher D_2 affinity – 80% compared to a D_1 occupancy of 30–40%. We found that *in vitro* assays at physiological temperature gave values which fitted with the PET data. Comparisons of affinities for various psychoactive drugs are usually made with values obtained at optimal temperature. In trying to make comparisons with clinical effects all of us should more consistently use data obtained at 37°C.

Bunney: I agree that we need to look carefully at affinities for a variety of receptors, but we must also remember that those receptors should have some physiological action. Until we find one for each of the receptors we are still in the dark.

Question: Can the serious relapses reported after withdrawal from clozapine be explained by these new concepts?

Bunney: Not in our model. We treated rats with antipsychotic drugs for seven months and looked at depolarisation block effects (Chiodo & Bunney, 1987). The animals return to normality about three weeks after discontinuation. We don't see an overshoot such as development of hyperactivity within the dopaminergic system.

Question: Are there any similarities between clozapine treatment and electroconvulsive therapy (ECT)?

Meltzer: I do not know of any direct comparisons. Max Fink suggested that ECT might be effective in treatment-resistant cases, and at our hospital we have used ECT for patients who refused clozapine or for whom it was unavailable. To my surprise, ECT has been effective; we have not seen the dramatic sustained improvement that we see with clozapine but I think it has some role in the treatment of schizophrenia.

Question: Anticholinergic drugs are known to worsen psychosis. Clozapine has strong anticholinergic effects. Has worsening of psychosis been seen with this drug? Anticholinergic drugs also cause delirious fits. To what extent has delirium been seen with clozapine?

Baldessarini: I am not aware of routine observations of worsening of psychosis with moderate to low doses of clozapine, but in Europe some years ago acute overdoses led to a form of delirium similar to that induced by other anticholinergic drugs. This responded to physostigmine treatment (Schuster *et al*, 1977). It is possible that at the upper end of the

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dose range, particularly with brain-damaged or elderly patients, aggressive use of clozapine might induce negative delirium-like phenomena.

Meltzer: There are reports of delirium with clozapine in elderly and Parkinsonian patients who received clozapine in the 200–300 mg range. These patients tolerate it well at lower doses. That is clearly an anticholinergic effect. We have not seen acute exacerbation of psychosis at the beginning of treatment with clozapine but we have seen people become delirious during treatment. When we discontinue the drug they recover.

Hippius: In Germany we have seen no exacerbation of psychosis after clozapine alone, but we do see dose-dependent occurrences of delirium in elderly patients if clozapine is combined with other drugs.

Question: In the classical theory of tardive dyskinesia (TD) it was claimed that two factors may produce worsening of the symptoms. One is increased dopamine function. The other is a decrease in the cholinergic system. If clozapine is producing a good firing of dopaminergic cells and is anticholinergic, how does this fit with the clinical observation of improvement in TD in patients treated with clozapine?

Gerlach: Clozapine does have an effect on TD in some cases, but it is not dramatic. This effect is not provided through the normal mechanism, namely the production of Parkinsonism. Because of the anticholinergic effect of clozapine there is not much Parkinsonism. There may be other mechanisms of action, such as a D_1 receptor-blocking effect, and improvement in the mental condition, and there might be a spontaneous TD recovery.

Bunney: I do not think we have the answer to this question. It is interesting that a patient with TD given clozapine seems to show improvement in TD symptoms. Psychosis may also improve at the same time. Since they already have TD, theoretically they must have had a good blockade of dopamine receptors some time in the past. This suggests that clozapine makes the patient better by some mechanism other than dopamine receptor blockade.

Baldessarini: I agree that we do not have a long-term explanation of why there is a low TD risk with clozapine. I would guess it is related to having a mild effect against dopamine. As to its acute effect in dyskinetic persons, one factor is that TD is notoriously related to the state of arousal and agitation of patients. Calming and lessening of psychotic irritability and arousal may contribute to milder manifestations of dyskinesia. Also the symptoms that seem to respond may be the dystonic forms of TD and it is well known that various dystonias may respond to anticholinergic therapies. That may also be part of the story.

Farde: When we discuss TD and various EPS we take for granted that these are neuroleptic-induced. Are the frequencies reported by Dr Naber consistent with the frequency in the untreated population?

Hippius: Studies in Switzerland suggest that 5% of untreated patients have disturbances similar to those seen later, at a higher incidence, under neuroleptic treatment.

Meltzer: There might be some clue from the studies in Parkinsonian patients who are psychotic because of L-DOPA or bromocryptine. If they are treated with low doses of thioridazine they become intolerably Parkinsonian. They are frozen at doses of 25–75 mg of thioridazine, which is almost as potent an anticholinergic as clozapine and produces the least EPS of classical neuroleptics. On the other hand, we can give those patients 25–50 mg of clozapine and block the psychosis, although we have increased dopaminergic activity from the L-DOPA or the bromocryptine, suggesting that even at low doses we are in some way blocking D_2 or perhaps D_4 receptors in the limbic system. We and others have observed improvement in the Parkinsonian symptoms in patients with Parkinson's disease. That may relate to Dr Ichikawa's finding (personal communication) that clozapine enhances the release of dopamine in the basal ganglia.

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