Psychopharmacology (1981) 73:184–187

Psychopharmacology

Clozapine: Plasma Levels and Prolactin Response

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Abstract. Serial plasma clozapine levels and serum prolactin levels were determined in two schizophrenic patients receiving clozapine, a novel antipsychotic drug. Despite marked therapeutic response and substantial clozapine blood levels, prolactin levels obtained 11–12 h after the last oral dose were unaffected or only minimally elevated. This confirms previous evidence of clozapine's unusal characteristics.

Key words: Clozapine – Schizophrenia – Prolactin – Serial plasma levels

The search for novel antipsychotic agents which may act differently from currently available neuroleptics remains of great importance. There is particular interest in identifying compounds which do not carry the risk of extrapyramidal side effects, particularly tardive dyskinesia. Clozapine, a dibenzodiazepine, has received considerable attention because of its antipsychotic efficacy, with little or no tendency to produce extrapyramidal side effects (Gross and Langner 1966; Berzewski et al. 1969; Simpson and Varga 1974; Matz et al. 1974; Gerlach et al. 1974). Unlike other antipsychotics, clozapine does not produce the same degree of catalepsy and it does not block apomorphine-induced stereotypy in animals, both generally considered manifestations of dopamine (DA) receptor blockade (Stille et al. 1971; York 1975). These findings have raised the possibility that clozapine's mechanism of antipsychotic action may not be dependent on blockade of DA receptors, as assumed in the DA hypothesis of schizophrenia. In vitro binding studies remain inconsistent with regard to clozapine's ability to block DA receptors (Burt et al. 1976; Leysen et al. 1978).

The ability of all previously studied clinically active neuroleptics to produce elevations in serum prolactin has been well-established (Langer et al. 1977; Meltzer et al. 1978) and is believed to result from DA receptor blockade in the pituitary (McCloud 1975). The degree of acute prolactin elevation in man following parenteral administration of neuroleptic drugs appears to be highly correlated with the milligram for milligram antipsychotic potency (Langer et al. 1977).

Meltzer et al. (1979a) reviewed eight studies involving clozapine and found a mean clinical antipsychotic dose of 241 ± 162 mg/day. In contrast, in 11 studies employing chlorpromazine, the mean dose was 691 ± 411 mg/day. Meltzer suggests, based on this comparison, that clozapine is approximately three times more potent than chlorpromazine as an antipsychotic agent and should, therefore increase prolactin at least as much, if not more than an equivalent dose of chlorpromazine.

Previous reports suggested that clozapine may cause no increase or only minimal increase in prolactin secretion in man. Sachar et al. (1976) reported that a single oral dose of clozapine (12.5 mg) in one normal subject, and 100 mg/day in two schizophrenic patients did not significantly increase their serum prolactin concentrations. Nair et al. (1979) treated ten schizophrenic males with clozapine for 3 days, reaching a maximum dose of 100 mg/day and a total of 200 mg during the study. They observed a small (17%) but statistically significant elevation in basal serum prolactin levels, but also observed a marked inhibition of growth hormone response to 0.75 mg apomorphine administered SC in six of seven subjects. These findings suggest that clozapine can block the DA receptors responsible for the apomorphine growth hormone effect without affecting the pituitary DA receptors involved in the prolactin response to the same degree. Meltzer et al. (1979a) suggest that this may indicate an important difference between the hypothalamic and pituitary DA receptors.

Meltzer et al. (1979a) reported on six male and seven female chronic schizophrenics treated with a mean daily clozapine dose of 458 ± 228 mg for females and 579 ± 216 mg for males, Baseline drug-free prolactin values were available for seven patients, and no significant increase in prolactin was observed during clozapine treatment (mean drug-free serum prolactin 59 ± 17 ng/ml, and during clozapine treatment, 57 ± 20 ng/ml). Among six patients without drug-free values the serum prolactin during clozapine treatment averaged 46 ± 22 ng/ml. Prolactin values in a sample of male and female patients receiving 800 mg chlorpromazine were significantly higher than values of male and female patients receiving clozapine. In addition, these investigators measured serum prolacin in four patients at 30-min intervals following clozapine administration (200–300 mg) for a 4-h period. All four patients had significant increases in prolactin, but the increase was slight and barely exceeded the 95% upper limit of normal values.

Since most of the studies with patients measured prolactin in samples taken in the morning, 10–12 h after the last dose of clozapine, it seemed possible that the lack of prolactin response might be related to low plasma levels of clozapine remaining at that time. This investigation was undertaken to examine the relationship between oral clozapine dosage, clozapine plasma levels, and prolactin response in two

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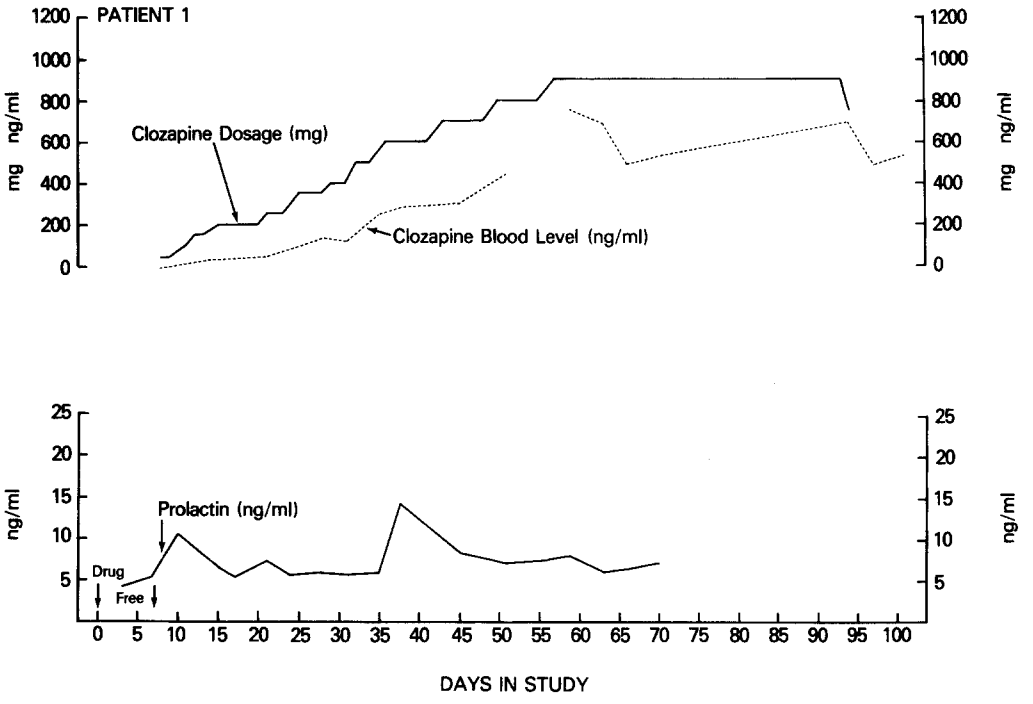

Fig. 1
Relationship of clozapine dosage (mg), clozapine blood level (ng/ml), and prolactin (ng/ml) in a schizophrenic (SCZ) patient

patients receiving increasing doses of clozapine over a 7-week period.

Materials and Methods

The subjects were two male chronic schizophrenic patients (30 and 35 years of age) who were diagnosed according to the Research Diagnostic Criteria of Spitzer et al. (1975). Both patients signed informed consent and were withdrawn from all antipsychotic medication for 1 week prior to receiving clozapine. Both patients were started on dosages of 20 mg twice daily and gradually increased over a 7-week period until 450 mg twice daily was administered. Medication was administered at 9 a.m. and 9 p.m. throughout. Blood samples for prolactin and clozapine were obtained between 8:30–9 a.m. (1–2 h after awakening) and prior to the morning dose. Baseline drug-free prolactin values were obtained just before initiation of clozapine treatment and twice weekly thereafter. Samples for clozapine plasma levels were obtained at the same time.

Samples for prolactin assay were promptly centrifuged, the plasma separated and stored frozen at −20° C to await analysis. All samples were analyzed in the same batch by radioimmunoassay (Sinha et al. 1973). Samples for clozapine assay were obtained in glass tubes with plastic screw caps without the use of vacutainers, centrifuged, and stored frozen. Assays used gas-liquid chromatography (Simpson and Cooper 1978). The method is sensitive enough to detect as little as 1 ng/ml in a 3 ml sample.

Clinical state was assessed weekly with the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham 1962).

Results

The time course of clozapine dosage escalation, clozapine plasma levels, and prolactin response are presented in Figs. 1 and 2. Significant amounts of clozapine were present 11–12 h after the last dose in both patients when receiving maximum doses of clozapine, and patient 2 had rather high clozapine blood levels (Simpson and Cooper 1978). In patient 1, prolactin concentrations remained only minimally elevated over baseline. The peaks occurring on two occasions may have been stress reactions of this extremely regressed and agitated patient.

Patient 2 initially showed prolactin response during doses up to 300 mg/day with blood levels up to 200 ng/ml. However, he then showed a consistent, modest prolactin elevation in response to daily clozapine doses of 500–700 mg, with plasma levels of 329–558 ng/ml. Interestingly, with dosages higher than 700 mg, yielding clozapine plasma levels well over 1000 ng/ml, the prolactin response returned to the normal range. The prolactin response this patient experienced was considerably less than the more than 40 ng/ml value obtained 12 h after receiving a 4 mg injection of thiothixene before the start of this study.

Both patients exhibited marked clinical improvement, as measured by BPRS ratings, during clozapine treatment. Therefore, minimal prolactin response occurred in the context of considerable antipsychotic effect.

Discussion

Clozapine appears to be less active in blocking pituitary DA receptors in humans then might be expected on the basis of its efficacy as an antipsychotic. Meltzer et al. (1979b) found that the IC_{50} (concentration producing a 50% inhibition) for clozapine for displacement of ^{3}H-spiroperidol from rat pituitary membranes is 1320 ± 86 nmol, compared to 72.6 ± 4.7 nmol for chlorpromazine. For all other neuroleptics, potency in displacement of spiroperidol correlates with clinical potency. The idiosyncratic nature of clozapine in this system, as well as in prolactin response, might suggest an antipsychotic effect less dependent on DA receptor blockade. It is also possible, however, that clozapine's action in mesolimbic or mesocortical dopaminergic tracts differs from its pituitary effects. Clozapine's effects on other neurotransmitters might also be involved in its apparently different effects on prolactin response (Meltzer et al. 1979b).

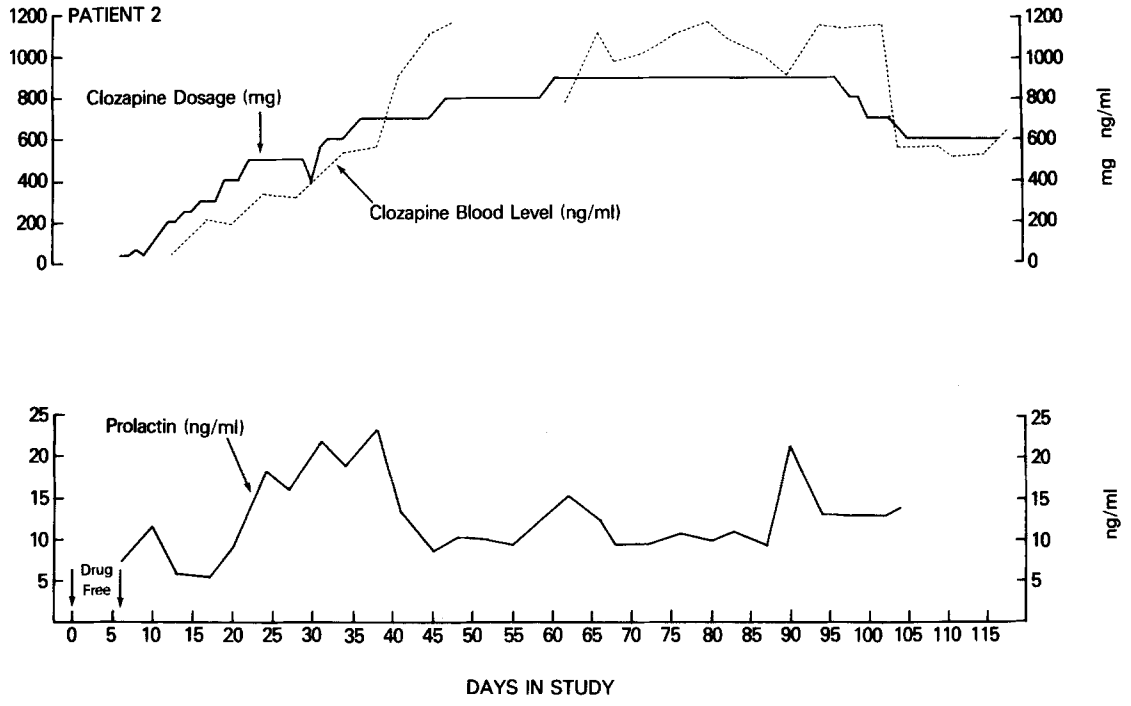

Fig. 2. Relationship of clozapine dosage (mg), clozapine blood level (ng/ml), and prolactin (ng/ml) in a schizophrenic (SCZ) patient

The apparent decrease of prolactin response with higher oral doses and higher plasma levels of clozapine is of considerable interest. This effect may have occurred without dosage increments and be due to some tolerance to antidopaminergic effects in the prolactin-regulating system. Significant prolactin elevations persisted for 2 weeks in patient 2, suggesting that if tolerance does develop it does so over this period.

Another explanation may be that clozapine exerts a biphasic effect with diminished prolactin response at higher blood levels. During the period when prolactin levels dropped considerably, the clozapine plasma levels of patient 2 had doubled (from 550–1100 ng/ml). Young and Meltzer (1980) described a similar phenomenon occurring with 2-chloro-11-3 dimethylaminopropylidene morphanthridene, a potential antipsychotic agent. In six of eleven patients studied, these authors found moderate increases in prolactin at lower doses with a return to baseline prolactin values as the dose was raised. They suggested that one possible explanation for this finding might be that the drug has only antidopaminergic effects at lower dosages, but also has some DA receptor-stimulating properties at higher dosages, or promotes DA release by some other mechanism.

Clozapine's proven antipsychotic efficacy, its apparent lack of extrapyramidal side effects, together with its unusual neuroendocrine profile continue to be of great scientific interest despite its clinical unavailability. It is hoped that a further understanding of its unusal clinical and neuropharmacologic characteristics will lead to the development of antipsychotic agents with a better benefit-to-risk ratio.

Acknowledgements. The work was supported in part by Public Health Service grant 5RO1-MH29841. The Hormone Distribution Program of the National Institute of Arthritis, Metabolism and Digestive Diseases provided the human prolactin and antihuman prolactin serum used in these studies.

References

Berzewski H, Helmchen M, Hippius H (1969) Das klinische Wirkungsspektrum eines neuen Dibenzdiazepin-Derivates. Arneim Forsch 19: 496–498

Burt DR, Creese I, Snyder SH (1976) Properties of [^{3}H] haloperidol and [^{3}H] dopamine binding associated with dopamine receptors in calf brain membranes. Mol Pharmacol 12:800–812

Creese I, Snyder SH (1977) A simple and sensitive radioreceptor assay for antischizophrenic drugs in blood. Nature 270:180–182

Gerlach J, Koppelhus P, Helweg E, Monrad A (1974) Clozapine and haloperidol in a single-blind cross-over trial: Therapeutic and biochemical aspects in the treatment of schizophrenia. Acta Psychiatr Scand 50:410–424

Gross H, Langner E (1966) Das Wirkungsprofil eines chemisch neuartigen Breitbandneuroleptikums der Dibenzodiazepingruppe. Wien Med Wochenschr 116:814–816

Langer G, Sachar EJ, Gruen PH, Halpern FS (1977) Human prolactin response to neuroleptic drugs is correlated with antischizophrenic potency. Nature 266:639–640

Leysen HE, Gommeren W, Laduron PM (1978) Spiperone: A ligand of choice for neuroleptic receptors. I. Kinetics and the characteristics of an in vitro binding. Biochem Pharmacol 27:307–316

MacLead RM (1976) Regulation of prolactin secretion. In: Martin L, Ganong WF (eds) Frontiers in neuroendocrinology. Raven, New York, p 169

Matz R, Rick W, Oh D. Thompson H, Gershon S (1974) Clozapine: A potential antipsychotic agent without extrapyramidal manifestation. Curr Ther Res 16:687–695

Meltzer HY, Goode DJ, Fang VS (1978) The effects of psychotropic drugs on endocrine function. I. Neuroleptics, precursors and agonist. In: Lipton MA, DiMascio A, Killam KF (eds) Psychopharmacology: A generation of progress. Raven, New York, p 509

Meltzer HY, Goode DJ, Schyve PM, Young M, Fang VS (1979a) Effect of clozapine on human serum prolactin levels. Am J Psychiatry 136:1550–1555

Meltzer HY, So R, Miller RJ (1979b) Comparison of the effects of substituted benzamides and standard neuroleptics on the binding of ^{3}H-spiroperidol in the rat pituitary and striatum with in vivo effects on rat prolactin secretion. Life Sci 573–584

Nair NPV, Lal P, Cervantes R, Yassa R, Guyda H (1979) Effect of clozapine on apomorphine-induced growth hormone secretion and serum prolactin concentration in schizophrenia. Neuropsychobiology 5:136–142

Overall JE, Gorham DR (1962) Brief psychiatric rating scale. Psychol Rep 10:799–812

Sachar EJ, Gruen PH, Altman N, Halpern FS, Frantz AG (1976) Use of neuroendocrine techniques in psychopharmacological research. In: Sachar EJ (ed) Hormones, behavior and psychopathology. Raven, New York, p 161

Simpson GM, Cooper TA (1978) Clozapine plasma levels and convulsions. Am J Psychiatry 135:99–100

Simpson GM, Varga E (1974) Clozapine: A new antipsychotic agent. Curr Ther Res 16:679–686

Sinha YN, Selby FW, Lewis UJ, Vanderlaan, WP (1973) A homologous radioimmunoassay for human prolactin. J Clin Endocrinol Metab 36:509–516

Spitzer RL, Endicott J, Robins E (1975) Research Diagnostic Criteria (RDC) for a selected group of functional disorders. New York State Psychiatric Institute, Biometric Research, New York

Stille G, Lauener H, Eichenberg E (1971) Pharmacology of 8-chloro-11-(4-methyl-l-piperazinyl)-5H-dibenzo [b, e] [1, 4] diazepine) (clozapine). Farmaco 26:603–625

York CN (1975) Amine receptors in CNS. II. Dopamine. In: Iversen LE, Iversen SD, Snyder SH (eds) Handbook of psychopharmacology. Biogenic amine receptors. Plenum, New York, p 23

Young MA, Meltzer HY (1980) RMI-81 582, a novel antipsychotic drug. Psychopharmacology 67:101–106

Received August 5, 1980; Final version October 22, 1980