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Adverse effects of clozapine

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Abstract. Adverse effects related to clozapine were assessed within a post-marketing drug surveillance program, the AMÜP study, in two university psychiatric departments. In a randomly selected sample of patients (intensive drug monitoring) ADRs of any type were observed in 76% of clozapine-treated inpatients. Sedation, hypersalivation, increase in transaminases, and EEG changes were most frequently observed, but only rarely required changes in therapy. In 8.1% of 959 patients exposed to clozapine in the total inpatient population of the participating hospitals ADR led to withdrawal of clozapine; in 3.9% reactions judged as severe and potentially life-threatening occurred. Among these latter toxic delirium prevailed. In addition, four cases of severe cardiovascular and respiratory dysregulation were observed with the combination of clozapine and benzodiazepines. These cases and one case of sudden death under clozapine and haloperidol treatment are presented in some detail. The results obtained for clozapine are compared to data from this drug surveillance program for other neuroleptics.

Key words: Clozapine adverse effects – AMÜP study – Clozapine + benzodiazepines

Adverse effects of psychotropic drugs are frequently discussed in the psychopharmacological literature. However, in contrast to the intensive research work concerning efficacy and mechanisms of action of psychotropic drugs, descriptions of their adverse effects are frequently insufficient, of non-specific nature or assessed in small and selected populations. Reliable data on type and frequency of adverse drug reactions (ADR) from prospective studies are urgently required for risk-benefit analyses. This became very obvious when the regionally restricted occurrence of agranulocytosis with clozapine (Idänpään – Heikkilä et al. 1977) prompted clozapine's withdrawal from the marked in several countries.

In this paper data on ADR with clozapine are presented derived from a prospective study of ADR to various psychotropic drugs, the AMÜP study (AMÜP = *A*rznei*m*ittel-*ü*berwachung in der *P*sychiatrie) (Rüther et al. 1980). Within this AMÜP study adverse drug reactions with psychotropic drugs have been continuously assessed since May 1979, with financial support of the German Federal Health Agency, the Bundesgesundheitsamt.

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Materials and methods

For the purpose of the study the following definitions have been used.

An adverse drug reaction (ADR) is defined as any drug-related manifestation in a patient that is unintended and undesired by the prescribing physician. Symptoms due to intoxication and inefficacy are not rated as ADR (Seidl et al. 1965).

Probability of a causal relationship between unwanted manifestation and treatment (Seidl et al. 1965; Hurwitz and Wade 1969):

Possible. Adverse reaction not characteristic for drug in question, and/or time sequence not in accordance with previous experience: or, probability of alternative cause for unwanted effect $>50\%$.

Probable. Adverse reaction to drug in question generally accepted; time sequence in accordance with previous experience; and probability of alternative cause $<50\%$.

Definite. In addition to the criteria necessary for a "probable" rank, reappearance of ADR following rechallenge with drug(s) in question is necessary.

Severity of ADR is implicitly determined by rating the impact on therapy of the ADR as follows:

Grade I. ADR leads to no change in medication;
Grade II. ADR leads to a change in medication consisting of dose reduction and/or additional treatment to counteract the ADR;
Grade III. ADR leads to discontinuation of the medication suspected of causing the ADR (including cases in which the drug would be discontinued if it were not vital).

In addition, a judgement is made on clinical grounds whether an ADR is severe or even life threatening.

For inpatient surveillance two different methods were used:

1. Intensive Drug Monitoring (IDM). With IDM a randomly selected sample of patients ($\sim$150 per year) were monitored for all ADR throughout their stay in hospital in the time period of May 1979–Dec. 1986.

2. Organized Spontaneous Reporting (OSR). With OSR only ADR grade III are assessed in all the other inpatients of participating hospitals.

Drug use per year has been continually assessed for the calculation of relative risk rates.

More detailed descriptions of the methodological approach were published earlier along with first results (Rüther et al. 1980; Grohmann et al. 1984; Schmidt et al. 1984).

In this paper results from IDM and OSR at the Psychiatric Departments of the Free University of Berlin and University of Munich covering the time period of May 1979–December 1986 are reported. If not explicitly stated otherwise, only ADR rated as probable or definite are included in this paper.

Results

In the participating hospitals as a rule clozapine is used only in treatment-resistant cases or in patients unable to tolerate other neuroleptics due to adverse effects. Thus, 959 patients in the Berlin and Munich hospitals were treated with clozapine, whereas haloperidol and perazine, the two most frequently used neuroleptics, were given to 4748 and 5229 patients, respectively. Clozapine was used mostly in schizophrenic patients. Eighty-two percent of all clozapine-exposed patients fell into this diagnostic category. The mean duration of treatment with clozapine (45 days) was longer than that with haloperidol (26 days) and perazine (27 days). The average daily dosage of clozapine was 188 mg compared to 290 mg for perazine.

As to concomitant treatment, data from IDM patients showed that clozapine was combined with other neuroleptics in 30% of clozapine patients for more than 1 week (in 59% even for at least 1 day), antidepressants were given in combination with clozapine only in 5%, benzodiazepines in 9% of clozapine patients for more than 1 week and in 20% for at least 1 day.

Intensive Drug Monitoring: frequency and type of ADR

As ADR observed with combination therapy frequently cannot be attributed to only one component of the combination, ADR rates for a single drug have to consider all ADR with involvement of this drug alone or in combination with other drugs and – separately – ADR attributed to the drug in question alone.

In 76% of clozapine patients ADR were observed at all (65% for clozapine alone). In 35% of patients ADR with involvement of clozapine (22% for clozapine imputed alone) had therapeutic consequences (grade 2/3) and in 17% of patients an ADR led to discontinuation of clozapine (9.0% for clozapine imputed alone).

Table 1 shows the types of ADR observed with clozapine in IDM. Sedation, the most frequent single ADR and mostly attributed to clozapine alone, required a change in medication only rarely. The same applies to gastrointestinal ADR (mostly hypersalivation and three cases of nausea), neurologic ADR (EEG changes, dysarthria, ataxia in one to two cases) and hepatic ADR (increase in transaminases, no cholostasis). Cardiovascular ADR, mainly orthostatic hypotension and dizziness, led to changes in therapy most frequently. Toxic delirium, observed in four patients and in one case with clozapine alone led to drug withdrawal in all four cases. Fever occurred only once in the 54 patients monitored.

Table 1. Types of ADR observed with clozapine (IDM, $n=54$)

ADR	All grades		Grade 2/3	
	All cases %	Clozapine imputed alone %	All cases %	Clozapine imputed alone %
Sedation	41	31	6	2
Gastrointestinal	33	30	11	7
Neurologic (excluding EPMS)	22	17	5	0
Hepatic	20	19	2	2
Cardiovascular	20	15	13	7
Toxic delirium	7	2	7	2
Fever	2	2	2	2

Table 2. ADR grade III observed with clozapine (IDM + OSR, $n=959$)

ADR	All cases	Clozapine imputed alone
Toxic delirium	2.7	1.8
Sedation	2.0	1.5
Cardiovascular	1.8	1.3
Hepatic	1.4	1.0
Gastrointestinal	1.1	1.0
Neurologic	1.0	0.6
Fever	0.6	0.6
Respiratory depression	0.4	0
Hematologic	0.2	0.2

ADR grade III (IDM + OSR)

ADR led to discontinuation of clozapine in 78 out of 959 patients (8.1%) treated with clozapine in the observation period. In 55 cases (5.7%) clozapine was imputed alone. Table 2 shows type and frequency of these ADR grade III. Toxic delirium was the most frequent adverse event, followed by sedation. Among cardiovascular ADR of grade III ranking third collapse was most frequent (0.7%). In addition, tachycardia and single cases of ventricular extrasystoles, hypertension and severe hypotension without collapse were observed. Increases in transaminases were observed as hepatic ADR, in one case accompanied by fever, leucocytosis, malaise and obstipation. Among gastrointestinal ADR severe hypersalivation led to clozapine withdrawal in 0.5%. In addition, some cases of nausea and, most important, two cases of subileus (once in combination with atropine) were observed. Neurologic ADR included some cases each of ataxia, dysarthria and EEG changes as well as three cases of grand mal seizures (twice with clozapine alone). Hematologic ADR were observed in two cases (one case of leucopenia and one case of eosinophilia). Agranulocytosis was not seen in this time period; only recently has one case occurred (see Grohmann et al. 1989). No case of

extrapyramidal ADR and no allergic skin reaction were observed.

Severe ADR

ADR rated as severe and potentially life-threatening were observed in 37 cases in all (3.9%) and in 20 cases attributed to clozapine alone (2.1%). These include all cases of toxic delirium and grand mal seizure (by definition rated as severe within the AMÜP study), the two cases of subileus, the case of leucopenia and one case of severe hypotension and collapse, followed by somnolence, dysarthria and hemiparesis observed with a combination of clozapine and two antihypertensives on the second day of treatment with this combination. Finally, four cases of severe adverse reactions were observed with clozapine in combination with benzodiazepines. These four cases are described in more detail below.

Case 1. A 29-year-old male manic patient, treated with 200 mg of clozapine in monotherapy for some weeks, finally increased to 250 mg. As non-compliance was suspected, 150 mg clozapine was given dissolved in water one evening; 18 h previously, the patient had received 30 mg flurazepam once. Two hours after the dissolved clozapine dose the patient suddenly fell to the ground, was unconscious briefly, then soporose. He was transferred to a medical intensive care unit and completely recovered some hours later. Intoxication with other drugs was excluded.

Case 2. A 34-year-old female schizophrenic patient. Treatment was begun with clozapine 25 mg plus lorazepam 1 mg twice on day 1. On the second day 2 h after the morning dose of 25 mg clozapine and 1 mg lorazepam the patient collapsed (RR 80/50 mm Hg) followed by respiratory arrest for about 30 s (observed by the nurses). The patient recovered in course of the next hour, but did not tolerate a second treatment course of clozapine 12.5 mg twice a day in combination with lorazepam over the next few days for recurring hypotension and pre-collapse. She was therefore switched to thioridazine + lorazepam, which she tolerated well.

Case 3. A 41-year-old male schizophrenic patient, treated with fluphenazin 6 mg + diazepam 2 mg + clobazam 20 mg + lormetazepam 1 mg for several weeks without therapeutic response. Fluphenazine was stopped therefore, and treatment with clozapine was begun; the BZD were continued. He received clozapine in a dose of 25 mg at noon and 100 mg at night; 3 h later toxic delirium developed together with severe hypersalivation. The patient collapsed (RR systolic 50 mm Hg, diastolic not measurable), respiratory arrest was observed and resuscitation begun. The patient was unconscious for about 30 min. He was transferred to the medical intensive care unit and recovered over the next 5 h. After some drug-free days clozapine was restarted in a 12.5 mg dose. With very slow increase in dosage and with a lower dose of concomitant BZD clozapine was tolerated well this time.

Case 4. A 52-year-old male schizophrenic patient, treated with butyrophenones in combination with diazepam without effect for several weeks. After another 3 weeks of diazepam monotherapy (10–30 mg) psychotic exacerbation prompted a clozapine trial. Diazepam was stopped and after 1 drug-free day a single dose of clozapine 25 mg was administered. Two hours later the patient collapsed and was unconscious for 10 min (RR systolic 60 mm Hg, diastolic not measurable, no pulse palpable, no recognizable respiratory activity). The patient recovered spontaneously. Later on, clozapine restarted at 12.5 mg with very slow increase in dosage and without further additional BZD was tolerated well.

In three of these four cases severe hypotension, respiratory depression and loss of consciousness, in one case only collapse and loss of consciousness are documented. All four patients had received BZD in combination with or immediately before clozapine treatment. As in several other cases of collapse observed with clozapine alone, no such severe complications ensued, an interaction of benzodiazepines and clozapine was suspected and the combination imputed. In relation to 189 patients exposed to this type of treatment a relative risk of 2.1% for this severe reaction results.

Fatal ADR

No fatal case was observed among the probable and definite ADR with clozapine involvement. In one patient sudden death was attributed as a "possible" ADR to a combination of clozapine and haloperidol. This patient, a 31-year-old schizophrenic female, had had surgery for on interatrial septal defect 13 years ago. She had been free of somatic symptoms ever since. She had been on continuous outpatient treatment with clozapine 200 mg for 2 years, initially combined with haloperidol 5 mg and biperiden 8 mg (all orally) for some months without ADR. Two days before readmission as an inpatient due to psychotic exacerbation, haloperidol 20 mg and biperiden 8 mg PO were added to clozapine 200 mg daily. On day 1 of inpatient treatment this drug regimen was continued, on day 2, she received haloperidol 10 mg PO and clozapine 100 mg IM in the morning. Four hours later she was found to be cyanotic with no recognizable respiratory activity and no palpable pulse. Resuscitation was begun and the patient was transferred to an intensive care unit. Artificial respiration had to be continued, but the patient remained comatose and died 4 days later. Autopsy was not performed. Toxicologic examinations did not reveal intake of any other substances.

Discussion

The data presented here on adverse reactions to clozapine derived from the AMÜP study give an example of post-marketing surveillance of psychotropic drugs in psychiatric inpatients even if the use of clozapine is restricted in the sense of a controlled release.

The overall frequency of ADR to clozapine observed with IDM (76% for all cases) is high but it is similar to the comparative rate for haloperidol (72%) observed within the AMÜP study. In comparison to perazine, another tricyclic neuroleptic of medium potency with an overall ADR frequency of 52%, clozapine was more frequently involved, whereas for ADR with therapeutic consequences rates for clozapine and perazine (35% and 28%) were similar and lower than for haloperidol (59%) (Grohmann et al. 1988).

Looking at all ADR, clozapine was mostly imputed alone. ADR with therapeutic relevance (grade II+III) and

ADR leading to drug withdrawal (grade III) were attributed to combinations of clozapine with other drugs in one third of all cases. Thus, combination imputations were less frequent for clozapine than for perazine, which may be due in part to the more frequent use of perazine in combination with other drugs (Müller-Spahn et al. 1988).

The most frequent types of ADR with clozapine, i.e. sedation, hypersalivation, EEG changes, increase in transaminases, only rarely gave rise to a change in clozapine treatment. This demonstrates that such global ADR rates have little clinical relevance. ADR enforcing drug withdrawal are of greater significance. As to grade III ADR, the rate observed with IDM was twice as high as that observed in all patients (monitored mostly with OSR). This may be due in part to the small sample size of IDM, in part to a closer monitoring of IDM patients and probably to some under-reporting in OSR as well.

The 8.1% ADR grade III observed in all inpatients leaves clozapine second after haloperidol (9.5%) in ADR grade III rates among neuroleptics (Grohmann et al. 1988).

The types of ADR differ widely for these two drugs, however. There is a complete lack of extrapyramidal reactions, which form the bulk of haloperidol's ADR grade III, with clozapine. In contrast, toxic delirium, the most common type of ADR grade III with clozapine, was observed more frequently with this drug alone (1.8%) than with any other psychotropic (Schmidt et al. 1987).

Severe and life-threatening ADR were considerably more frequent with clozapine (3.9% for all clozapine cases, 2.1% for clozapine imputed alone) than with haloperidol (1.3% for all cases, 0.2% alone) or perazine (0.3% for all cases, 0.2% alone) (Grohmann et al. 1988). This difference is not explained by the high frequency of toxic delirium with clozapine alone; higher relative frequencies for grand mal seizure (0.3% for clozapine versus 0.01% for perazine) and for subileus (0.2% versus 0.06%) as well as the cardiorespiratory reactions to clozapine/benzodiazepine combinations all contribute to the higher total figure for clozapine. However, such comparisons must be viewed with some caution because of the different sample sizes (less than 1000 patients for clozapine, about 5000 patients for haloperidol and perazine). In addition, the population of clozapine patients is selected for treatment resistance or intolerance of other neuroleptics. These patients represent a more severely ill group, and they may differ in their susceptibility to any ADR.

As to the combination of clozapine with BZD, the experience from the AMÜP study shows that particularly in the case of acute treatment (initiation of clozapine following pretreatment with BZD or together with BZD) severe cardiovascular and respiratory dysregulation may ensue. A relative risk of 2.1% was observed for this severe reaction.

The available information does not allow any reliable conclusions concerning the pathophysiology of sudden death in the one patient who died under treatment with clozapine and haloperidol. The corrected interatrial septal defect probably constituted a pre-existing risk factor. This calls for most careful monitoring of patients with a cardiac history of any sort if clozapine is used. Whether the IM administration of clozapine – unique in this patient on the day of the fatal complication – was of particular relevance must remain open to speculation.

In conclusion, these data on frequency, type and clinical relevance of ADR observed with clozapine within the AMÜP study show on one hand that clozapine is a compound to be used with caution and skill; its risks are not limited to hematological problems alone. On the other hand it is a particularly valuable drug, and its lack of extrapyramidal reactions which so frequently cause severe problems with other neuroleptics was demonstrated again here.

Thus, clozapine is a particularly good example of how careful ADR assessment within a post-marketing drug surveillance scheme can lead to better recognition of specific risks and benefits of different drugs and from there to better management of drug-related risks.

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