Eur Arch Psychiatr Neurol Sci (1988) 237:223–229

European Archives of Psychiatry and Neurological Sciences

© Springer-Verlag 1988

Clinical and Neurobiological Findings in Children Suffering from Tic Disease Following Treatment with Tiapride

Ch. Eggers, A. Rothenberger, and U. Berghaus

Klinik für Kinder- und Jugendpsychiatrie, Universitätsklinikum Essen, Hufelandstrasse 55, D-4300 Essen 1, Federal Republic of Germany

Summary. Tiapride, a substituted benzamide derivative, possesses good clinical antidyskinetic properties due to its DA_2-blocking activities. It has been shown to be clinically effective in the treatment of tic disease in children. In order to study tiapride's antidyskinetic properties in the treatment of the tic syndrome in children, we conducted a simple, placebo-controlled study on 10 children followed by a double-blind cross-over study on 17 children. Tiapride was shown to have a positive therapeutic effect on tics in children; whereas it has no adverse effects on neuropsychologically measurable cognitive performances in children. Neurophysiological parameters such as the EEG frequency analysis and sensory evoked potentials were not affected by tiapride, nor was the neurosecretory, hypothalamic-hypophyseal regulation of the sex hormones, thyroid stimulating hormone, growth hormone, or thyroid hormone impaired. The hyperprolactinemia caused by tiapride's dopaminergic properties was moderate and restricted to the duration of therapy.

Key words: Gilles de la Tourette-Syndrome – DA_2-blocker – Neuropharmacology – Hypothalamic-pituitary-thyroid axis

Introduction

According to the common definition by the American child psychiatrist Kanner (1957), tics are short, sudden, and frequently repetitive movements of groups of muscles and do not serve any apparent purpose. The time sequence of the movements is irregular. Generally, only head and shoulder areas are involved in simple tics. The most common tic is the blinking tic. The phenomenology can be manifold and varied. Blinking, widely opening one's eyes, squinting, sniffing, clicking, burping, clearing one's throat, and various forms of grimacing occur in the facial area alone. Additional groups of muscles are involved when the severity of tic symptoms increases. Vocal tics can also occur. Tics are intensified during excitement; they are hardly, if at all, observable during sleep. A child can only suppress tics for a short period.

Diagnoses have been made in accordance with the ICD no. 307.2 (first axis according to Rutter et al. 1976). Epidemiological studies have shown that tic disorders can be expected in approximately 5% of all school children, with the frequency among boys being twice that of girls (v. Harnack 1958; Pringle et al. 1967). In the Mannheim epidemiological study, tics were observed in approximately 8% of the 8 year olds (Rothenberger 1984). Only a small proportion of children with tics are seen by a child psychiatrist. They account for between 1% and 7% of a child psychiatrist's patient (Remschmidt and Remschmidt 1974; Torup 1962; Zausmer 1954). Of 600 children examined for the first time in our outpatient department over the course of 1 year, 27 (4.5%) had tics (Eggers 1982).

Due to the frequency and severity of some tic forms, in particular Gilles de la Tourette Syndrome, the search for an effective therapy is especially important. Tics have a multifactorial etiology and may therefore require not only a psychotherapeutic approach, but pharmacological therapy as well. In some tics disorders a partial organic cause can be assumed; disturbances in the field of dopaminergic extrapyramidal-motor structures, in particular in the nigrostriatal area, are primary considerations.

Offprint requests to: C. Eggers

There are four arguments in favor of a disturbance in the field of dopaminergic functions: (1) dopamine receptor-blocking substances have a therapeutic effect on the tic syndrome, (2) stimulants leading to increased dopamine release can provoke or intensify tics, (3) lowered homovanillic acid values are found in the CSF of tic patients, and (4) tic symptoms can occur when long-term therapy with neuroleptic drugs is discontinued.

For these reasons, haloperidol, a potent dopamine receptor-blocking agent, has preferentially been administered to children and adolescents. Recent research results now enable us to distinguish various dopaminergic receptors. On the basis of studies by Costall and Naylor (1979, 1983), two different dopamine receptors are responsible for involuntary abnormal movements: DA_1 neurons, whose stimulation induces a relatively nonspecific hyperactivity, and DA_2 neurons, whose stimulation causes dyskinetic reactions, particularly in the oro-linguo-facial region. DA_2 neurons have been shown to be specifically influenced by DA_2 blockers such as pimozide, a diphenylbutyl-piperidine derivative, or by the benzamide derivative tiapride. In animal experiments, these substances antagonize the dyskinetic oro-linguo-facial symptoms which can be triggered by injections of dopamine in the striate body. Haloperidol, however, is a strong DA_1 blocker. It acts primarily on the dopaminergic meso-limbic system also resulting in a strong antipsychotic effect, whereas tiapride does not possess any antipsychotic properties.

Methods

A total of 27 children (25 boys and 2 girls) with multiple tics and Gilles de la Tourette Syndrome were treated with tiapride, a benzamide derivative with DA_2-blocking antidyskinetic properties. The average age was 12.5 (7–18) years. Ten children participated in a placebo-controlled preliminary pilot study and the remaining 17 took part in a three-phase double-blind cross-over study. The dose was 5 mg/kg body weight in the first and 6 mg/kg body weight in the second study.

During the first study, performed under inpatient conditions in our hospital, the tics were counted three times daily for 15 min at meal times, and towards the end of each period (3 days baseline, 7 days each in the placebo and tiapride phases and 6 months of outpatient tiapride treatment followed by 3 days hospitalization at the end of this period), they were also rated in 30-min play and test situations. At the end of each period various blood parameters were measured (blood count, liver function, kidney function, prolactin, growth hormone follicle stimulating hormone, lutenizing hormone, triiodothyronine, thyroxine, and thyrotropic hormone. The following test procedures were also carried out: critical fusion frequency; continuous performance test (vigilance); simple and complex reaction times; tapping (both hands); ECG, EEG, event-related potentials (sensory, visual, and acoustic).

A clear reduction in tic frequency was seen in the 10 children during the course of the entire observation period. During baseline, placebo, and tiapride phases the tic frequency of each patient was rated and averaged over a 15-min observation period. Mean rates were: baseline $\bar{x} = 22$, placebo $\bar{x} = 16$, tiapride $\bar{x} = 8$. This difference in tic frequency between the different phases may be considered to be significant at the 5% level (Kruskal-Wallis test – χ^2 approximation $\chi^2 = 5.30$; $P = 0.0427$). In 6 patients a reevaluation of tic frequency after 6 months of tiapride treatment was possible: the mean tic rate in these children was $\bar{x} = 14$. Because of the small number of probands no statistics were computed.

Aiming for better evaluation of the efficacy of tiapride on tics, the second study, a three-phase double-blind cross-over study, on an additional 17 children was performed. These children were randomized in two groups. The first phase (M 0) lasted for 6 weeks. It consisted of a 2-week inpatient and a 4-week outpatient phase without medication. In the following phase (M 1) lasting 10 weeks, one group of children was treated with tiapride (6 mg/kg body weight), and the second group was given placebo. The medication was reversed in the third phase (also 10 weeks, M 2): the placebo group was given tiapride and the tiapride group a placebo. Thus, the whole study had a duration of 26 weeks and a total of three phases (M 0, M 1, M 2). To evaluate the tics, the children were observed for 30 min at play (a total of six times in the 2-week inpatient phase with no medication and once a week in the outpatient phase). Video recordings were made and used as questionnaires for the parents and teachers to evaluate the frequency, variety, and intensity of the tics. Seven blood samples taken in each of phases M 1 and M 2 served to determine the drug and prolactin levels. Other clinical parameters (blood count, liver and kidney functions) were measured at the beginning of the M 0 phase and at the end of phases M 1 and M 2.

Results

In the 17 children with multiple tics who participated in the double-blind cross-over study, as usual, the head and shoulder region was the most affected. Nearly all children presented facial tics (blinking, facial twitches). Vocal tics (barking, screaming, clearing one's throat, grunting) were observed in 10 children (59%). One child presented coprolalia. The distribution of tic forms in the 17 children is shown in Fig. 1.

One of the 17 children ($-1\,n$) had to drop out of the study in the first phase (without medication), since open treatment with tiapride became necessary due to considerable intensification of the tics. The remaining 16 children formed two groups each of 8 children. Group-1 received tiapride in phase M 1 and a placebo in phase M 2. The children in group-2 were given a placebo in the M 1 phase and were treated with tiapride in the M 2 phase.

All of the children in group-2 were able to complete the study. However, in 4 children of group-1 a drastic increase in the tic frequency was observed at the change-over from M 1 to M 2 in the double-blind study, so that they also had to be treated openly with

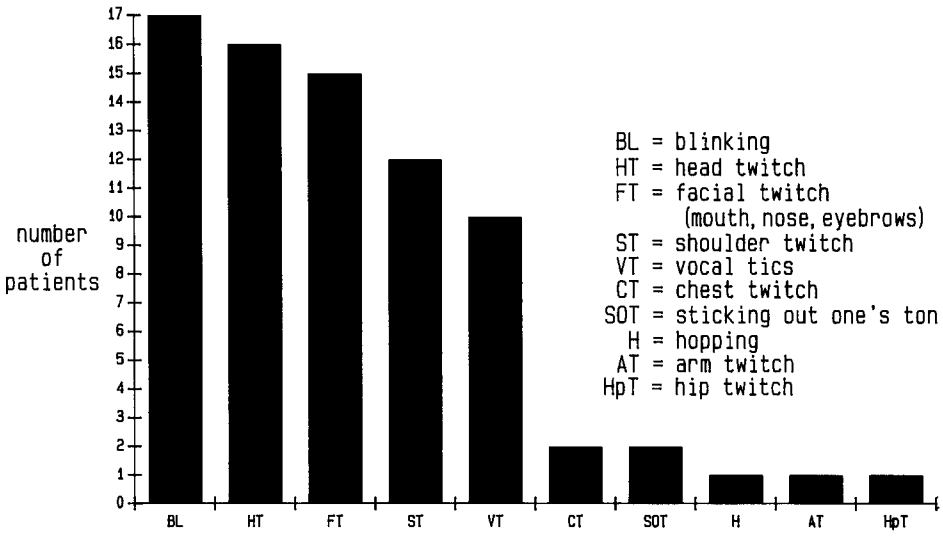

Fig. 1. Tic form distribution amongst the patients

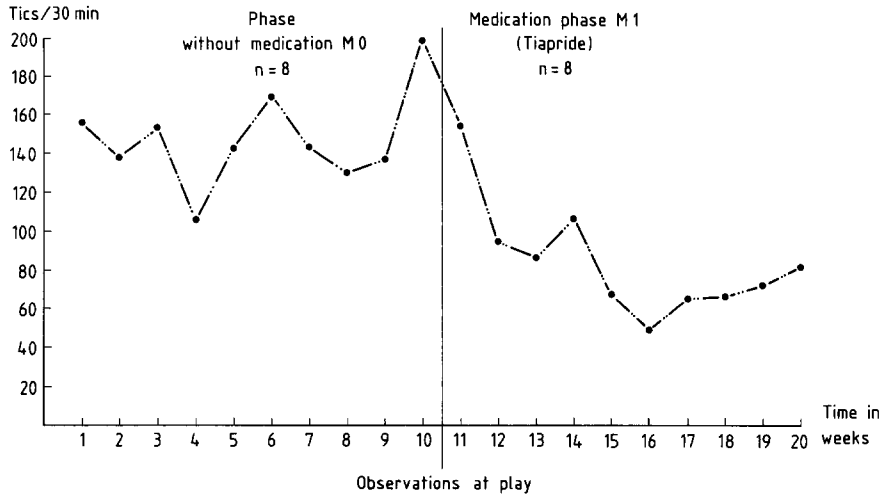

Fig. 2. Mean tic rates in group-1 during the M 0 and M 1 phases

tiapride. These 4 children belonged to group-1; i.e., they had initially received tiapride and were then given a placebo and reacted with an increase in tics. This indicates the drug's efficacy in the treatment of the tic syndrome. In the group which initially received tiapride, there was clear reduction in the tic frequency during the administration of tiapride. Following the M 0 phase (without medication), the mean tic rate was almost halved (from 152.4 ± 42.2 tics in 30 min to 85.3 ± 29.7 tics in 30 min). Figure 2 presents the mean tic rates for all children in group-1 in phase M 0 (no medication) and phase M 1 (tiapride). A clear reduction in the tic frequency can be seen during tiapride therapy. The results were statistically significant ($P = 0.01$; Friedmann's analysis of the variance in ranked data; $P = 0.05$; Wilcoxon-Wilcox pairwise comparison).

On the other hand, the mean tic rates of the 8 children who first received the placebo and then tiapride (group-2) did not differ significantly in the three phases of the double-blind cross-over study. Tiapride treatment reduced the mean tic frequency by nearly one-fifth of the original values measured in the drug-free and placebo phases [e.g., the mean tic rates of the children in group-2 during M 0 was 156.8 ± 50.8 tics in 30 min, during M 1 (placebo) 150.8 ± 52.7, and during M 2 (tiapride) 125.0 ± 40.8 tics in 30 min]. The difference was not statistically significant, however.

Wilcoxon's U test was used to check the comparability of the tic rates in groups 1 and 2 in the initial situation (M 0) without medication. No differences were found and thus, both groups were comparable with respect to tic rates.

Of the 5 children who had to drop out of the study due to a drastic increase in the tic frequency, 4 were followed for a period of about 6 months at an outpatient visit once a month. They were observed for

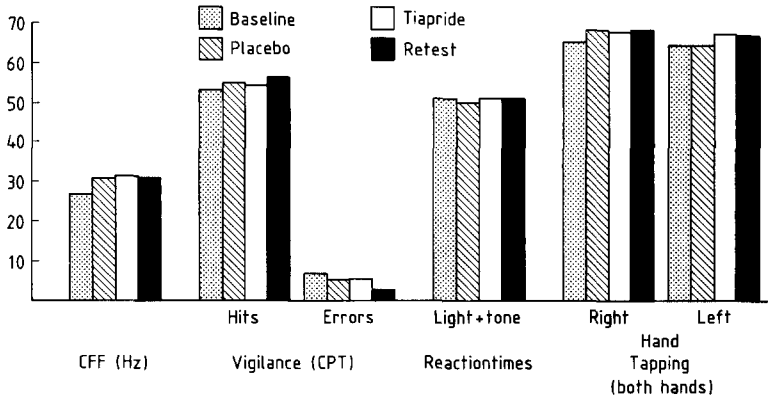

Fig. 3. CFF = critical fusion frequency. CPT = continous performance test (Vigilance Test). Reaction times = measured by the Wiener Reaktionsgerät. Tapping = motor tapping with both hands for evaluation fine motor accuracy. There were no significant differences between the different examination periods (baseline, placebo, short- and long-term tiapride therapy)

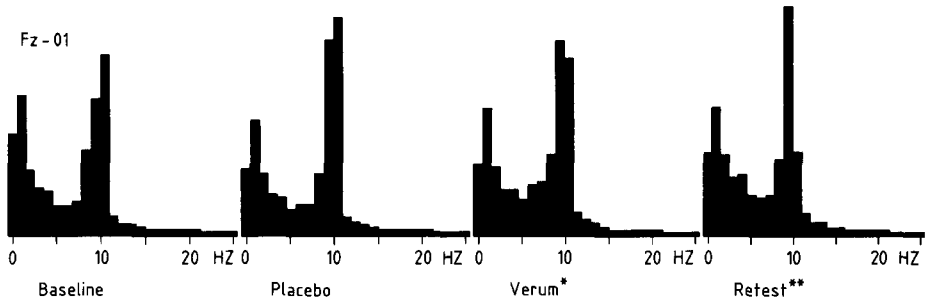

Fig. 4. Grand average of power spectra of all 10 children of the first study during phases 1 to 4. * 6 days treatment with tiapride. ** Reexamination after 6 months treatment with tiapride

30 min while playing with their parents, and a blood sample was obtained to measure drug and prolactin levels. All 4 children were initially treated openly with high doses of tiapride (up to 900 mg/day), and 2 of these children reacted successfully to this high-dose tiapride therapy; they had already responded well to the medication with tiapride (M 1). Both the tic frequency and the sound volume of the particularly burdening vocalization tics were reduced considerably following continued open treatment with high doses of tiapride. In the further course of treatment, however, the efficacy of the drug decreased, thus making it necessary to administer 1 mg initially and then 2 mg pimozide, which, however could not satisfactorily influence the tic symptoms. The other 2 children, who were treated openly with tiapride after dropping out of the study, required up to 3 mg pimozide daily after rather a short time. There was a 70% to 80% reduction in the tic frequency as compared to the time prior to the study.

The side-effects of tiapride therapy proved to be slight. However, in the first few weeks of therapy, nearly all of the children complained of being tired. Two children gained up to 10 kg within 18 months. This was caused by a clear increase in their appetite. One of these children was also given pimozide during this period. No changes occurred with respect to blood count, transaminases, lactate dehydrogenase, alkaline phosphatase, urea, creatinine, uric acid, electrolytes, fats, blood sugar, and protein electrophoresis. The only long-term side effect observed in our clinic was weight gain in some patients.

The neuropsychological examinations including various vigilance and attention tests, reaction time measurements, flicker fusion threshold and fine motor tests showed that tiapride had no influence on attentiveness, vigilance, visual discrimination capacity, reaction speed and fine motor response, intelligence, and memory. All of these functions remained fully unimpaired, both during short- and long-term tiapride therapy when compared with the medication-free and placebo phases. This is shown in Fig. 3. There were no significant differences between the neuropsychological findings at the end of the different examination periods.

This is of utmost importance for a child whose neural functions are still developing. The fact that the cognitive functions of the children studied while taking tiapride remained unimpaired is in good agreement with our neurophysiological findings. When a frequency analysis of the children's EEGs was made, only very slight, if any, changes were seen during long- and short-term tiapride treatment when compared with the placebo and medication-free phases (Fig. 4). The children's event-related potentials (visual, acoustic, sensory) were not affected by tiapride (Fig. 5), nor where there any changes in latencies or amplitudes in the various study and treatment phases. Figure 5 shows a grand average of all visual and sensory evoked potential curves for the 10 children in

the first study in all four phases (baseline, placebo, 6 days tiapride, 6 months tiapride) demonstrating the lack of significant changes with respect to latency periods, amplitudes, and the curves in any of the phases.

Recent studies have shown that tiapride promotes prolactin secretion in adults (Chouza et al. 1982; Gennari et al. 1981; L'Hermite et al. 1978; 1979). However, only very little is known about tiapride's endocrinological side-effects in children. For this reason, we studied the serum levels of the following hormones at the end of the placebo phase, the 7 days and 6 months tiapride therapy, and after discontinuing therapy with tiapride: prolactin, luteinizing hormone, follicle stimulating hormone, triiodothyronine, thyroxine, thyrotropic hormone, and growth hormone (somatotropic hormone). Thyrotropic hormone (thyrotropin), growth hormone, and prolactin were measured prior to and following stimulation with 200 µg thyrotropin releasing hormone. The Wilcoxon and Student's *t*-test were used for the statistical evaluation. Tiapride was shown to have no negative effects on the hypothalamic-hypophyseal regulation of the sex hormones, growth hormone, or thyroid hormones. The corresponding hormone levels (with and without stimulation) were within normal ranges during all of the study phases.

Due to tiapride's antidopaminergic effect, however, there was an increase in prolactin secretion resulting in hyperprolactinemia. The mean prolactin levels for the 27 children of the total sample were 36.6 (first study) and 37.7 ng/ml (second study). Elevated prolactin was found a few days after drug administration had been initiated (Fig. 6). The prolactin levels returned to normal 4 weeks after tiapride was discontinued. There was a linear correlation between tiapride and prolactin levels ($r = 0.78$ and 0.81; $P = 0.0001$). There was no correlation, however, between the prolactin or drug levels and the tic frequency.

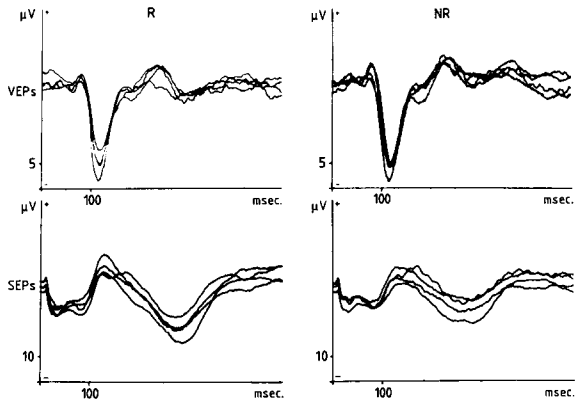

Fig. 5. Grand average of visual evoked potentials of all 10 children during phases 1 to 4* (FZ − 01; s = 40). R = random, Nr = nonrandom condition. * phase 1: baseline; phase 2: placebo; phase 3: 6 days tiapride therapy; phase 4: 6 months tiapride therapy

Discussion

The results of the preliminary placebo-controlled pilot study and those obtained in group-1 of the double-blind cross-over study clearly indicate a tiapride effect in reducing tic frequency. Because of the only slight short- and long-term side effects, tiapride may be considered as a good candidate for efficient therapy of tic disease and Gilles de la Tourette Syndrome in children. The objection to its use with regard to our findings was the insufficient reduction of tic frequency in group-2 (children receiving placebo and then tiapride). This may be interpreted as a consequence of inadequate dosage, the low number of patients, and an order effect. Taking into considera-

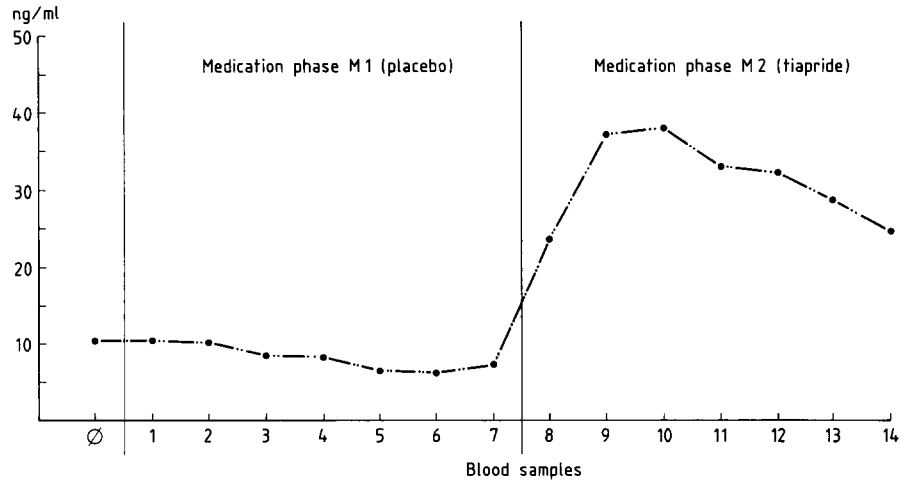

Fig. 6. Mean prolactin levels in group-2. ∅: baseline prolactin value in the phase without medication = M 0. The prolactin values of group-2 children are presented in ng/ml during the course of tiapride and placebo therapy. There is a slight decrease in the prolactin level in the placebo phase and a clear increase when tiapride is administered

tion the other results of our two studies, our clinical experience, and the neuropharmacological concept that tiapride is an efficient DA_2 blocker, the order effect may be ruled out. Nevertheless, the aim of future studies must be to add further data in order to clarify the outstanding question.

Insufficient therapeutic success or declining efficacy indicate combination with other DA_2-blocking substances such as pimozide. As well as other authors (Regeur et al. 1986; Shapiro and Shapiro 1984) we observed that pimozide is an effective drug for the treatment of tic disease in children showing fewer side effects than haloperidol. To date, we have no clinical experience with clonidine, an α_2 receptor agonist.

Tiapride's antidyskinetic properties are caused by its DA_2-blocking activity in the nigrostriatal system. The hyperprolactinemia observed in the children receiving tiapride treatment may indicate that tiapride also acts on the pituitary lactotrophs. This possibly means that the dopaminergic action of dopamine on the DA_2 receptor of the pituitary lactotrophs is impaired by tiapride. This impairment is likely to be the result of steric antagonism of dopamine and tiapride at the DA_2 receptor. This is supported by in vitro and in vivo observations indicating that the prolactin inhibiting action of dopamine is blocked by tiapride (L'Hermite et al. 1978, 1979).

It should be noted that in the 10 children in the first study there was a significantly lower prolactin level after 6 months of tiapride therapy as compared to the mean prolactin level during the 7 days therapy (30 ng/ml vs 36.6 ng/ml ± 4.63 ng/ml; statistically significant on the 1% level in accordance with the Wilcoxon test). This is in agreement with the worsening of the tic symptoms following the initially successful tiapride treatment in some of our patients. The decrease in the serum prolactin levels following long-term therapy with tiapride could be due to the fact that dopaminergic lactotrophic cells develop tolerance to the prolactin secretion promoting effect of tiapride. The increase in tic frequency following the initial clinical improvement achieved with tiapride could similarly be due to the fact that the dopaminergic nigrostriate neurons develop tolerance to tiapride. There could possibly even be a numerical increase in dopaminergic receptors during long-term tiapride therapy, as has been demonstrated in animal experiments following long-term administration of neuroleptic drugs including sulpiride, a benzamide derivative (Burt et al. 1977; Fuxe et al. 1980; Memo et al. 1981). The sudden increase in tic rate in some patients at the cross-over point from tiapride to placebo in the double-blind cross-over study provides evidence for possible sensitization of DA_2 receptors.

Tiapride did not exhibit any adverse effects on the secretion of gonadotropins, growth hormone, or thyroid hormones. Unlike other antidopaminergic drugs and in particular other benzamide derivatives such as sulpiride, tiapride does not appear to influence thyrotropin secretion (Eggers et al. 1983). Thyrotropin secretion is regulated physiologically by dopamine and is thus influenced by dopamine-blocking substances. After administering sulpiride to adults, for example, there is an increase in thyrotropin secretion following stimulation with thyrotropin releasing hormone (Portioli et al. 1976).

Another interesting difference between tiapride and sulpiride is the fact that tiapride had no effect on the amplitudes and latent periods of event-related potentials; while sulpiride has a very clear effect thereon, as do other neuroleptic drugs (Brosteanu and Floru 1980; Saletu 1977; Shagass 1981). These differences indicate that tiapride acts in a different way to conventional neuroleptic drugs, at least at the neurophysiological level. This is even more surprising since tiapride, like antipsychotic drugs, is capable of increasing the dopamine turnover in the limbic system although it does not have antipsychotic properties (Fuxe et al. 1983). The clinical, neurophysiological, and neuroendocrinological differences between the two benzamide derivatives sulpiride and tiapride can be best explained by the possibility of differential affinities to various dopaminergic receptors.

References

Brosteanu EF, Floru L (1980) Untersuchung der visuell evozierten Potentiale bei schizophrenen Patienten unter einer Behandlung mit Sulpirid. Arzneimittelforsch 30:1305–1309

Burt DR, Creese J, Snyder SH (1977) Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. Science 196:326–328

Chouza C, Romero S, Lorenzo J, Camano JL, Fontana AP, Alterwain P, Cibils D, Gaudiano J, Feres S, Solana J (1982) Traitement des dyskinésies par le tiapride. Sem Hôp (Paris) 58:725–733

Costall B, Naylor RJ (1979) Behavioural aspects of dopamine agonists and antagonists. In: Horn AS, Korf J, Westerrink BH (Hrsg) The neurobiology of dopamine. Academic Press, London New York San Francisco

Costall B, Naylor RJ (1983) The substituted benzamides: Selective dopamine receptor blockade. In: Ackenheil M, Matussek N (Hrsg) Special aspects of psychopharmacology. Expansion Scientifique Francaise, Paris

Eggers Ch (1982) Pathophysiologie von Tic-Erkrankungen. Psychophysiologische und neurophysiologische Untersuchungsmethoden – Erfahrungen mit Tiapridex in der Therapie des Tic-Syndroms. In: Aschoff JC (Hrsg) Die Therapie extrapyramidal-motorischer Erkrankungen. Schattauer, Stuttgart

Eggers Ch, Olbricht T, Rothenberger A (1983) Neurobiological findings in children with tics and Gilles de la Tourette

syndrome. In: Ackenheil M, Matussek N (eds) Special aspects of psychopharmacology. Expansion Scientifique Francaise, Paris

Fuxe K, Ögren SO, Hall H, Agnati LF, Andersson K, Köhler C, Schwarcz R (1980) Effects of chronic treatment with L-sulpiride and haloperidol on central monoaminergic mechanisms. In: Cattabani F (Hrsg) Long-term effects of neuroleptics. Raven Press, NewYork

Fuxe K, Agnati LF, Andersson K, Calza L, Benfenati F, Zini I, Battistini N, Köhler C, Ögren SO, Hökfelt T (1983) Analysis of transmitter-identified neurons by morphometry and quantitative microfluorimetry. Evaluation of the actions of psychoactive drugs, especially sulpiride. In: Ackenheil M, Matussek N (Hrsg) Special aspects of psychopharmacology. Expansion Scientifique Francaise, Paris

Gennari C, Nami R, Pizzuti M, D'Ascenzo G, Bianchini C (1981) Effets du tiapride en perfusion sur le taux plasmatique de bêta-endorphine, prolactine et dopamine chez des patients souffrant d'algies cancéreuses. Sem Hôp (Paris) 57:795–800

Harnack GA von (1958) Nervöse Verhaltensstörungen beim Schulkind. Thieme, Stuttgart

Kanner L (1957) Child psychiatry. Thomas, Springfield/III

L'Hermite M, McLeod RM, Robyn C (1978) Effects of two substituted benzamides, tiapride and sultopride, on gonadotrophins and prolactin. Acta Endocrinol 89:29–36

L'Hermite M, Michaux-Duchêne A, Robyn C (1979) Tiapride-induced chronic hyperprolactinaemia: interference with the human menstrual cycle. Acta Endocrinol 92:214–227

Memo M, Battaini F, Spano PF, Trabucchi M (1981) Sulpiride and the role of dopaminergic receptor blockade in the antipsychotic activity of neuroleptics. Acta Psychiatr Scand 63:314–324

Portioli I, Modena G, Fantesini C, Bellefelli A, Dotti C (1976) Interelations TRH-sulpiride sur la sécrétion de prolactine. Nouv Presse Méd 5:931

Pringle ML, Butler NR, Davie R (1967) 11000 seven year olds. National Bureau for corporation in child. Case, London

Regeur L, Pakkenberg B, Fog R, Pakkenberg H (1986) Clinical features and long-term treatment with pimozide in 65 patients with Gilles de la Tourette's syndrome. J Neurol Neurosurg Psychiatr 49:791–795

Remschmidt H, Remschmidt U (1974) Symptomatologie, Verlauf und Prognose von Tic-Erkrankungen im Kindes- und Jugendalter. Klin Pädiatr 186:185–199

Rothenberger A (1984) Therapie der Tic-Störungen. Z Kinder-Jugendpsychiatr 12:284–301

Rutter M, Shaffer D, Sturge C (1976) A guide to a multi-axial classification scheme for psychiatric disorders in childhood and adolescence. Institute of psychiatry, London

Saletu B (1977) Cerebral evoked potentials in psychopharmacology. In: Desmedt JE (Hrsg) Auditory evoked potentials in man. Psychopharmacology correlates of EP's. Karger, Basel (Prog Clin Neurophysiol, vol 2) pp 175–207

Shagass C (1981) Psychotropic drugs and evoked potentials, paper presented at the Xth International Congress of Electroencephalography and Clinical Neurophysiology, Kyoto, Japan

Shapiro AK, Shapiro E (1984) Controlled Study of Pimozide vs. Placebo in Tourette's Syndrome. J Am Acad Child Psychiatr 23:161–173

Torup E (1962) A follow-up study of children with tics. Acta Paediatr 51:261–268

Zausmer RCM (1954) Treatment of tics in childhood. Arch Dis Child 29:537–542

Received May 4, 1988