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ORIGINAL PAPER

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Clinical effects of COX-2 inhibitors on cognition in schizophrenia

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Abstract An activation of pro-inflammatory cytokines in the central nervous system is associated with cognitive disturbances. This process is mediated by prostaglandins and cyclo-oxygenase-2 (COX-2). COX-2 inhibitors have been suggested to show beneficial effects in disorders associated with cognitive disturbance, although clinical effects on cognition have not been shown until today. Data from a schizophrenia study were reevaluated under the aspect whether an effect on the positive and negative syndrome scale (PANSS) factor cognition can be observed during therapy with the COX-2 inhibitor celecoxib add on to risperidone in comparison to riperidone alone. Beside the effect on the PANSS total score, the effect on the cognition factor was the most pronounced using the analysis of covariance compared to all other factors of the PANSS ($p < 0.06$). Although suggestions of basic research led to an expected therapeutic effect of COX-2 inhibitors on cognition, this effect could not yet be shown clinically. In schizophrenia, the effect on cognition contributes to the therapeutic effect of COX-2 inhibitors.

Key words cognition · COX-2 inhibition · inflammation · schizophrenia · dementia

Introduction

Recent work focusses on the question whether an inflammatory or even infectious process is involved in the pathogenesis of impaired cognitive function both in patients (Dickerson et al. 2003) and in healthy people (Teunissen et al. 2003).

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The suggestion of an inflammatory mechanism in the pathogenesis of Alzheimer's disease (AD) has stimulated this discussion. In AD observational epidemiological studies have revealed that anti-inflammatory treatments can attenuate or prevent the symptoms (McGeer 2000). Several neuropathological studies have supported this claim by showing a role for inflammatory and immune mechanisms in AD, including findings of reactive microglia within or near AD lesions. Nevertheless, clinical trials designed to inhibit inflammation by inhibiting cyclo-oxygenase-2 (COX-2) activity have failed in the treatment of AD (Aisen et al. 2003). Whether methodological problems of the studies such as duration of the disease, duration of treatment, or the outcome variables are responsible for this lack of clinical effects is a matter of discussion (Launer 2003).

An important contribution to this discussion can be the answer to the question whether COX-2 inhibitors have a clinical effect on cognitive function. We could show that COX-2 inhibitors have a clinical effect in schizophrenia (Müller et al. 2002), a disorder where the cognitive decline is one of the core symptoms and which therefore was called 'dementia praecox' by Emil Kraepelin (Kraepelin 1899). The data were reanalyzed in particular under the aspect whether the COX-2 inhibitor celecoxib attenuates cognitive impairment in schizophrenic patients.

Patients and methods

The methodology of the study is described elsewhere in detail (Müller et al. 2002). Briefly, 50 schizophrenic patients were included in the prospective, randomized, double-blind study of celecoxib therapy add-on to risperidone in acute schizophrenia. A total of 25 (11 f, 14 m) patients were assigned to the celecoxib and risperidone group, and 25 (14 f, 11 m) to the risperidone and placebo group. The treatment period during the trial lasted for 35 days (5 weeks). Assessments of psychopathology were performed at weekly intervals, using the positive and negative syndrome scale (PANSS).

The dosage of risperidone ranged between 2 and 6 mg/day. The dosage of celecoxib was 2×200 mg/day (morning and evening). The age of the patients was between 18 and 65 years, whereby the mean

age was 35.9 (SD = 12.8) years in the celecoxib group and 35.5 (SD = 13.6) years in the placebo group. Statistics were performed according to the criterion of last observation carried forward.

This new statistical (re-)analysis (post hoc analysis of the clinical response to celecoxib) was performed according to the five-factor model of the PANS scale (Lindenmayer et al. 1994). This widely accepted model consists of a five-factor interpretation of the PANSS. These five factors reflect the negative, positive, excitement, cognitive, and depression/anxiety domains of psychopathology. The analyses of covariance (ANCOVAs) for all factor scales were calculated identical in design to the one used for the original scale (Müller et al. 2002). In order to evaluate further the components, which contribute to the effect of celecoxib to cognition, an item analysis of the cognition factor was performed.

Results

The results of the ANCOVAs, calculated with treatment as a group factor, five visits under treatment as a time factor, and the baseline visit as covariate are shown for all five factors and the PANSS total scale (Table 1).

As described earlier, a significant effect of the celecoxib add-on therapy on the total PANSS score was seen. We also observed an effect with a tendency for significance ($p \leq 0.06$) on the cognition factor. No statistical significant effect was seen on the other PANSS factors.

This item analysis shows that two items contribute mostly to the result of the cognition factor: the items 'difficulty in abstract thinking' (item ANCOVA $p \leq 0.06$) and 'conceptual disorganization' ($p \leq 0.09$) (item 5 negative subscale 5 and item 2 positive subscale). The other items 'mannerism and posturing', 'disorientation', and 'poor attention' (general subscale 5, 10, 11; $p \leq 0.27$, $p \leq 0.52$, $p \leq 0.34$) contribute nearly nothing. This can be interpreted in the way that COX-2 inhibition probably influences conceptual and abstract thinking, not other aspects of cognition.

Discussion

Frontal cortex, amygdala, and hippocampus are structures of the CNS, which are critically involved in cognitive function and in memory. These structures also show constitutive COX-2 expression (Yamagata et al. 1993; Breder and Saper 1996; Kaufmann et al. 1996). Therefore it has been suggested that COX-2 is involved in cognitive function. Animal models of the cognitive system, in particular of learning and memory, are the models of long-term potentiation (LTP) and long-term depression (LTD) (Bliss and Collingridge 1993; Malenka 1994). Using these models it has been shown that COX-2 has an inhibitory role in the LTP function, while pharmacological COX-2 inhibition directly attenuates LTP in the dentate gyrus of the hippocampus (Murray and O'Connor 2003). In parallel, COX-2 inhibition attenuates LTD in the CA1 region of the hippocampus (Murray and O'-Connor 2003). These neurophysiological data point to an important role of COX-2 inhibitors in learning and memory.

Table 1 Results of the ANCOVA using the five factors model and the PANSS total score

PANSS (Factor) scale	Group effect (mean improvement under treatment)		
	F	df	p
Positive s.	1.29	1, 47	0.26
Negative s.	1.42	1, 47	0.24
Cognition	3.64	1, 47	0.06
Excitement	2.04	1, 47	0.16
Depression	0.33	1, 47	0.57
Total PANSS	3.80	1, 47	0.05

It is known, however, that cognitive functions are mediated by the cholinergic neurotransmitter system. In a rat model of CNS inflammation it has been shown that the selective COX-2 inhibitor rofecoxib suppresses the inflammatory reaction in the brain and prevents a loss of cholinergic neurons (Scali et al. 2003). In addition, cholinergic hypofunction was significantly attenuated by treatment with rofecoxib (Giovanni et al. 2002). Moreover, it has been observed that transgenic mice with a neuronal overexpression of COX-2 develop a deficit in memory (and changes in behavior) (Andreasson et al. 2001).

According to these data from basic research a therapeutic effect of COX-2 inhibitors on cognition would be expected, but was not observed in clinical studies with patients suffering from AD. In schizophrenia, however, the cognition factor shows the most pronounced general effect of the five PANNS factors. Although this effect is not statistically significant possibly due to the small statistical power of 25 patients, it shows a trend to significance, while the other factors do not show any significant results. Although many aspects contribute to the effect of celecoxib in schizophrenia, the effect to cognition seems the strongest single effect that could be identified. The item analysis shows that items, which reflect the thinking process per se (conceptualization and abstract thinking), not items such as attention or orientation contribute to the effect of celecoxib in schizophrenia.

Effects of COX-2 inhibitors to symptoms of depression would be expected from a theoretical point of view and a clinical study in patients suffering from osteoarthritis has shown an antidepressive effect of the COX-2 inhibitor rofecoxib (Collantes-Estevez and Fernandez-Perez 2003). Therefore it has to be discussed whether methodological aspects, such as the short duration of the study, a clinical ceiling effect, or the fact that the depression factor in schizophrenia might reflect a specific type of affective disturbance, can explain the lack of effects of COX-2 inhibition to the depression factor in this study.

We found in our study that the clinical effect of celecoxib over the five weeks treatment period is better in patients with a shorter duration of the schizophrenic

disease (data not shown). Therefore it can be suggested that the long-lasting biological process leading to cognitive disturbance in a chronic disorder such as AD might explain the lack of clinical effects of COX-2 inhibitors in AD. It has to be studied whether an early treatment of cognitive disturbances in different disorders shows therapeutic effects of COX-2 inhibitors.

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