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The AMPA Antagonist ZK 200775 in Patients with Acute Ischaemic Stroke: A Double-Blind, Multicentre, Placebo-Controlled Safety and Tolerability Study

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Stroke · AMPA antagonist · Glasgow Coma Scale · NIHSS · Blood pressure

Abstract
Background and Purpose: ZK 200775 is a selective competitive AMPA receptor antagonist. It has demonstrated neuroprotective efficacy in experimental models of stroke and tolerability in healthy volunteers. We tested the safety and tolerability of ZK 200775 in patients with acute ischaemic stroke. ***Methods:*** In a multicentre double-blind, randomised, placebo-controlled phase II trial, 61 ischaemic stroke patients were treated with either placebo or active drug in a dose finding design. Twenty-five patients received placebo, 12 patients received a total dose of 262.5 mg in 48 h (group 1) and 13 patients received a total dose of 525 mg in 48 h (group 2), and 11 patients received a total dose of 105 mg over a period of 6 h (group 3). We studied the pharmacokinetics of the compound and the effect of the infusion on the neurologic and haemodynamic parameters of the patients. The study was not powered to detect neuroprotective efficacy. ***Results:*** In group 2 there was a significant transient worsening in the mean NIH stroke scale score 14–18 h after the start of treatment. This was due to reduction of consciousness (stupor and coma) in 8 out of 13 patients. Level of consciousness improved approximately 6 h after cessation of infusion. No significant haemodynamic responses were observed. Even after reduction of the administered dose and duration of infusion to 6 h (group 3), 2 patients experienced a reduction in level of consciousness. The effect of ZK 200775 on level of consciousness gave cause for concern and the trial was stopped prematurely for safety reasons. ***Conclusions:*** The AMPA antagonist ZK 200775 reversibly worsened the neurological condition in patients with acute ischaemic stroke. Our results suggest that ZK 200775 exerts significant sedative effects in patients with acute stroke which preclude its further development as a neuroprotective agent in this indication.

Introduction

Glutamate is the major excitatory neurotransmitter in the mammalian brain. Its effects are mediated mainly by the glutamate receptor subtypes N-methyl-*D*-aspartate (NMDA) and α-amino-3-hydroxyl-5-methyl-isoxazole

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propionate (AMPA). Selective antagonists of both NMDA and AMPA subtypes have been developed as potential therapeutic agents for acute ischaemic stroke. Antagonists of both NMDA [1] and AMPA [2] receptors have demonstrated neuroprotective effects in animal models of focal cerebral ischaemia. Agitation has been observed following administration of NMDA antagonists to animals [1]; no similar effects have been observed with preclinical studies of AMPA antagonists [2].

ZK 200775 is a selective competitive AMPA receptor antagonist. Its biochemical and pharmacological profile is similar to that of the compound 2,3-dihydroxy-6-nitro-7-sulphamoyl-benzo(f)quinoxaline (NBQX) which has shown substantial neuroprotective effects in animal models of cerebral ischaemia [3]. ZK 200775 is neuroprotective in both in vitro and in vivo models of cerebral ischaemia and has a superior side effect profile compared with NBQX [4, 5]. Toxicological studies of ZK 200775 in rats revealed hypotonia, lethargy, and slow respiration at higher dosages (6 mg/kg/h as a continuous IV infusion over 4 weeks). Median lethal dose after single intravenous injection of ZK 200775 in mice and rats was approximately 50 mg/kg. A single intravenous injection of 25 mg/kg did not produce any mortality in rats, mice or dogs. In contrast to certain NMDA antagonists neither neuronal vacuolisation nor necrosis was observed in rat toxicology studies.

Early Clinical Studies of ZK 200775

The clinical pharmacology of ZK 200775 in healthy subjects has been investigated in two studies. In the first study [6], 42 healthy elderly male volunteers received an intravenous infusion of between 0.06 mg/kg and 6 mg/kg of ZK 200775 over 4 h. The most commonly reported adverse effects were CNS-related: sedation, disturbances of perception, memory and equilibrium were observed. The CNS-related effects were dose dependent and were observed following doses higher than 0.12 mg/kg.

No relevant effects on temperature or respiration rate were observed. In the highest dose group there was an asymptomatic increase in both systolic and diastolic blood pressure of 10 mm Hg.

The second study [7, 8] examined the safety of a 24-hour infusion of ZK 200775, (alone or in combination with an initial 30 min loading infusion) in 32 healthy elderly men. Based on pharmacokinetic modelling, the concept of a loading dose was introduced to ensure blood-brain-barrier penetration leading as quickly as possible to neuroprotective substance levels within the supposed 6-hour therapeutic time window. Infusion rates of 0.075, 0.15 and 0.3 mg/kg/h were sustained for 24 h. Similar dose-dependent side-effects were observed. All three infusion rates were deemed safe, the maximum tolerable dose for a 24 h infusion was considered to be 0.3 mg/kg/h. No clinically relevant changes in laboratory parameters or vital signs were observed within the 7-day observation period.

Subjects and Methods

Study Design and Objectives

We assessed the safety, tolerability and pharmacokinetics of ascending doses of ZK 200775 via continuous infusion in patients with acute ischaemic stroke. Neurological and functional outcome data were collected but the study was not designed to detect neuroprotective efficacy.

Approval for the study was gained from local ethical committees at all centres. Patients gave written, witnessed informed consent wherever possible, with independent witnessed verbal consent from patients unable to write. If the patient was unable to give consent verbally, written informed assent was accepted from the next of kin or close family member.

The study adopted a sequential dose escalation design and was conducted in 11 centres in Europe between August 1997 and August 1998. At each dose step 18 patients were randomly assigned to either ZK 200775 or placebo with a ratio of 2:1. After each dose group had been completed, interim safety analysis was performed before proceeding to the next dose increment. The study remained double-blind within each dose step. Between dose steps the study was unblinded only for the safety board members and biostatisticians. After the second dose step it was decided not to increase the dose but to change the design for dose group 3. Based on the evaluation of safety data of dose groups 1 and 2, and brain pharmacokinetic simulations, it was deemed necessary to treat patients using a reduced infusion time/total dose scheme. A reduction of infusion time from 48 h to 6 h was considered rather conservative with regard to safety. Measurement points were added in the first 6 h after the start of the infusion and the level of consciousness assessed using the Glasgow Coma Scale (GCS). Twenty-four patients were randomly assigned in a 1:1 ratio to either ZK 200775 or placebo. The ratio was changed to improve power to detect reduced conscious level between active and placebo groups in this phase. Randomisation was stratified according to the total NIHSS score at baseline.

Patients over 18 years of age presenting with acute ischaemic stroke within 24 h of onset of symptoms were eligible for inclusion. Female patients were ineligible unless they had passed beyond menopause or had been surgically sterilised. Patients with very mild (NIHSS <2) or severe (NIHSS >21) stroke were excluded from the study, as were patients with known severe renal, cardiac or neurological disease. CT scan of brain was required before the start of treatment; findings consistent with a diagnosis of acute ischaemic stroke were required for eligibility.

For dose group 3, additional exclusion criteria relating to GCS were employed. Patients with eye opening <3, best verbal response <4 or best motor response <4 were considered ineligible.

Immediately before the start of the infusion, blood samples were drawn for clinical chemistry, haematology, and pharmacokinetic

Table 1. Loading and maintenance doses

	Dose mg/h	Infusion rate, ml/h	Volume ml	Dose mg
Dose group 1				
Loading	50	10	5	25
Maintenance	5	1	47.5	237.5
Total dose				262.5
Dose group 2				
Loading	100	20	10	50
Maintenance	10	2	95	475
Total dose				525
Dose group 3				
Loading	100	20	10	50
Maintenance	10	2	11	55
Total dose				105

Table 2. Patient demographics

	Placebo	Dose group		
		1	2	3
Patients	25	12	13	11
Mean age, years	67.5	65.9	69.7	63.1
Age range	39–85	52–82	55–85	35–78
Mean height, cm	166.6	174.8	169.1	173.6
Mean weight, kg	75.4	82.6	75.0	81.3
Mean baseline NIHSS	6.2	4.0	8.3	7.3
Seven-day Barthel	79.2	93.3	44.6	72.7
Four-week Barthel	87.0	95.0	62.9	80.5

analysis. Routine observations (temperature, blood pressure, oxygen saturation, respiration rate and 12 lead ECG) were recorded. In dose group 3 the baseline GCS was assessed.

A fixed dose was used for each dosage group. Group 1 received 262.5 mg over 48 h, group 2 received a total dose of 525 mg over 48 h and patients in group 3 received a total dose of 105 mg over a period of 6 h. ZK 200775 was administered as an intravenous loading infusion over 30 min followed by a maintenance infusion over 47.5 h (groups 1 and 2) or 5.5 h (group 3). Loading and maintenance doses are shown in table 1. During the infusion, heart rhythm, body temperature, blood pressure, respiration rate and oxygen saturation were recorded at 30 min intervals for the first 4 h, thereafter at hourly intervals. Twelve-lead ECG was performed at 30 min, 4, 24 and 48, 72 and 96 h after the start of the infusion. Continuous Holter ECG monitoring was performed for 72 h after infusion. In group 3, GCS was assessed hourly during the infusion and then every 2 h up to 24 h, thereafter every 4 h up to 48 h, further at 72 and 96 h, at 7 days and after 4 weeks. If the level of consciousness fell during the monitoring period, GCS was re-assessed every 4 h until recovery. In all 3 dose groups, routine checks for adverse events were made at 0.5, 1, 4, 6, 8, 12, 24, 48, 72 and 96 h after commencement of infusion. Blood samples for pharmacokinetic analysis were drawn at 0.5, 12, 24, 36, 48, 48.5, 50, 52, 56 and 60 h after the start of the infusion. Blood for clinical chemistry and haematology was drawn at baseline, 24, 48, 72 and 96 h.

At 7–10 days after recruitment the first follow-up visit was made. NIH stroke scale, Barthel index, modified Rankin score, clinical chemistry, haematology, 12-lead ECG, adverse events and blood pressure were recorded. A final visit was made 4 weeks after recruitment, during which the parameters measured at the first follow-up visit were re-recorded.

Estimation of ZK 200775 in blood was performed using a validated normal-phase HPLC method after solid-phase extraction of the samples. Maximum plasma concentration at the end of the loading dose, steady-state plasma concentration and total clearance of the drug from plasma were derived from the plasma concentration data.

Comparison between treatment groups was made using two-sided statistical tests. A one-way analysis of variance was applied to continuous data such as the NIH stroke score; Kruskal-Wallis tests were applied to ordinal data. Pharmacokinetic parameters were used as covariates in the evaluation of dose-response relationships.

Since this was the first safety study of ZK 200775 in patients, no data upon which a power calculation could be based were available. The sample size was therefore determined pragmatically by experts referring partly to probability tables to detect differences in adverse events rates.

Results

Patient Demographics and Protocol Compliance

A total of 63 Caucasian patients with acute ischaemic stroke were enrolled in 11 centres; 4 centres in Germany, 3 in Finland and one each in Belgium, France, Great Britain and the Netherlands. Two patients did not receive any trial infusion hence the analysis is based upon 61 recipients of trial infusion. Patient demographics are shown in table 2.

Safety and Tolerability

Four deaths occurred during the study, two in the treated group and two in the placebo group. All deaths were attributable to stroke or related vascular disease or complications common in stroke patients. The two deaths in the placebo group were attributed to myocardial infarction (3 weeks after randomisation) and recurrent cerebral infarction (12 days after randomisation), respectively, both confirmed by post-mortem examination. One patient in dose group 2 died of cerebral oedema 4 days after presentation with large cerebral infarction. No post-mortem examination was performed. One patient in dose

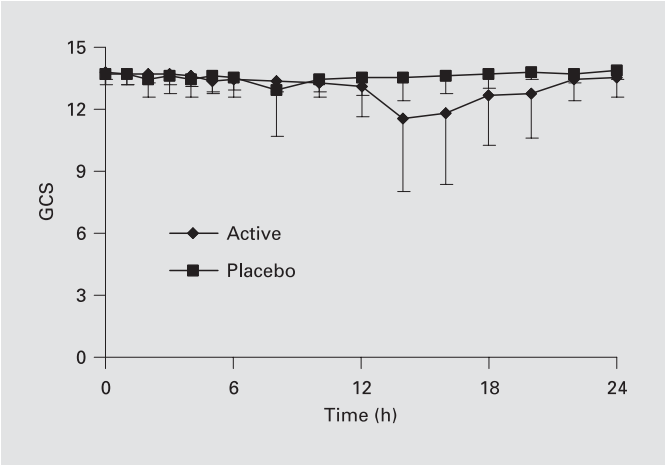

Fig. 1. Changes in GCS based on patients from dose group 3 with active drug vs. placebo from 0 to 24 h (error bars represent ±1 SD).

group 3 died of pneumonia 8 days after initiation of trial infusion. Post-mortem confirmed extensive pneumonia as the cause of death: no evidence of aspiration was seen. Serious adverse events were reported in 18 of 36 active patients (50%) and 4 of 25 placebo recipients (16%). Serious adverse events occurred in 3 of 12 (25%) of patients in dosage group 1, 11 of 13 (85%) of patients in group 2, and in 4 of 11 (36%) of patients in group 3. Disturbance of conscious level was the most commonly encountered serious adverse event. Eleven patients in group 2 experienced severe disturbance of level of consciousness, and two of the three serious adverse events in group 1 were related to less severe reductions in level of consciousness. Diminution in responsiveness was reported in only 1 patient in the pooled placebo group. The onset of reduced conscious level was usually more than 24 h after the start of the infusion; however, three patients had loss of consciousness within the first 12 h of drug infusion. Although other causes may have explained loss of consciousness in these 3 patients, these events were attributed to the study drug infusion by the study director. Recovery after cessation of infusion was slow (6–24 h) in all cases.

Patients in dose group 3 received the same rate of infusion as dose group 2 but over a shorter duration. Somnolence occurred in 5 of 11 patients, and profound deterioration of conscious level (GCS falling below 8) was recorded in 2 patients. The time course of fluctuation in GCS in placebo and active treatment patients in dose group 3 over the first 24 h is shown in figure 1. The obvious onset of reduced level of consciousness was seen at approximately 14 h after commencement of the 6-hour maintenance infusion. The level of consciousness improved over approximately 6–42 h (not shown) following cessation of infusion. Depression of respiration requiring intervention was not observed in any patient.

Other serious adverse events possibly related to the infusion in the 3 dose groups comprised nystagmus and dysarthria (1 patient in dose group 1), hypotension (1 patient in dose group 2), confusion (1 patient in dose group 2) and ataxia (1 patient in dose group 2). All episodes occurred during the infusion and resolved within 24 h of cessation of infusion.

Other Adverse Events and Premature Discontinuation of Study Medication

Sensory disturbance, confusion, dysarthria, visual blurring, nausea and vomiting were all recorded more frequently in recipients of drug than in recipients of placebo. The incidence of adverse events was greatest towards the end of the maintenance infusion, and adverse events occurred more commonly in dose group 2 than in the other treatment groups. Study medication was prematurely discontinued due to adverse or serious adverse events in 11 of 61 patients (18%). Premature discontinuation occurred in 9 of the 13 patients in dose group 2. One patient each in the placebo and dose group 3 cohorts had study medication discontinued.

Pharmacokinetic Analysis

The mean steady state concentration increased from 2.29 ± 0.79 μmol/l in group 1 to 5.81 ± 1.89 μmol/l in group 2. In group 3 the mean plasma concentration at the end of the loading infusion was similar to group 2. Mean plasma concentration in group 3 patients at the end of the 6-hour maintenance infusion was 6.62 ± 3.48 μmol/l, similar to the mean steady state concentration measured in group 2. The area under concentration/time curve increased in proportion with total administered dose.

Haemodynamic and Electrocardiographic Effects

No significant changes in mean arterial blood pressure were observed within or between groups (fig. 2). A non-significant increase in corrected QT interval was seen in dose group 3. No trend in heart rate was observed in any dosage group.

Clinical Laboratory Evaluation

No study drug-related changes in clinical chemistry or haematological parameters were noted.

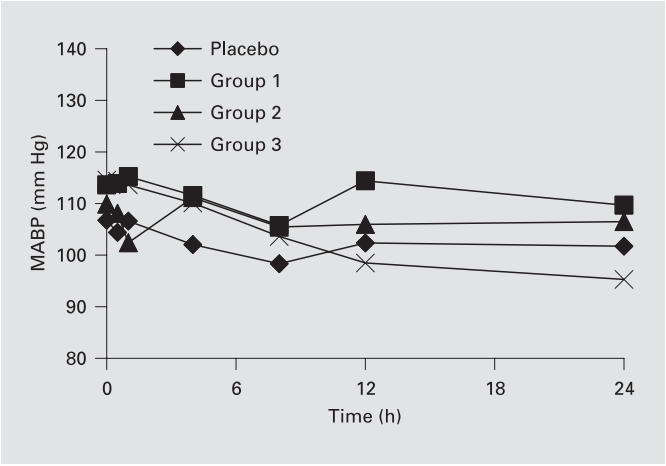

Fig. 2. Mean arterial blood pressure (MABP) in placebo and dose groups 1, 2 and 3 from 0 to 24 h.

Outcome

The study was designed to assess safety rather than efficacy of the compound; therefore, as expected, no significant differences in NIH score, Barthel score or modified Rankin score were seen between groups after 4 weeks.

Discussion

The pharmacokinetics of ZK 200775 in stroke patients were consistent with those measured following shorter term administration to healthy volunteers. It is known from in vitro investigations that a 400 nmol/l concentration of ZK 200775 is necessary to occupy 90% of neuronal AMPA receptors. Assuming 85% of circulating ZK 200775 is bound to plasma proteins, a plasma concentration of 2.67 μmol/l would result in 90% receptor occupancy under equilibrium conditions. This was regarded as the target plasma concentration of ZK 200775, and was consistently achieved and maintained in dosage groups 2 and 3. Slower elimination has been shown in a recent study of the pharmacokinetics of ZK 200775 in patients with mild renal impairment [9].

Safety

Dose group 1 appeared to show no clear increase in CNS adverse events, but in dose group 2 there was a marked increase of the number of patients experiencing reductions in level of consciousness under active treatment. Sedation and psychomimetic effects have been observed with other CNS glutamate antagonists such as aptiganel [10] and selfotel [11], and suggest successful penetration of the blood brain barrier. Although some CNS-related adverse effects were predicted from earlier clinical studies in healthy volunteers, the frequency and severity of these effects was greater in stroke patients than in healthy subjects. Although this finding has not been fully explained, this increased sensitivity to CNS-related adverse effects may be attributable to greater tissue bioavailability due to blood-brain barrier disruption, to altered AMPA receptor activity following ischaemic stroke, or to differences in dose and duration of infusion, as the healthy volunteers received lower doses infused over shorter periods. As a high proportion of patients in this study had relatively mild stroke with little clinical evidence of cortical involvement, the latter explanation seems most likely. The onset of stupor or coma typically occurred more than 24 h after commencement of infusion but 3 patients became unconscious within the first 12 h of drug administration. Disturbance of conscious level during prolonged infusion was the major safety concern and after independent safety review and approval, prompted use of a shorter duration of infusion and regular monitoring of conscious level in dose group 3. Despite this, reduced level of consciousness was again a problem. Events were most pronounced between 14–18 h after the start of infusion. This does not reflect the time course of plasma kinetics, but would seem to mirror the time-course of pharmacokinetic/pharmacodynamic simulations of concentrations in the central compartment [12] based on EEG parameters in healthy volunteers. It suggests that, due to the slow diffusion of the drug into the brain and a prolonged half-life of elimination from the brain [12], the maximum concentration of drug within brain tissue can be reached approximately 12 h after commencement of the dosing protocol employed in group 3. Time courses of adverse events in the studies with patients and healthy volunteers support the concept of extremely retarded entry and elimination half-lives of ZK 200775 in brain tissues [12, 13]. In all clinical studies of ZK 200775 significant depression of conscious level was observed at relatively lower dosages than suggested by preclinical experiments. Doses tolerated by healthy volunteers were not tolerated by stroke patients. The difficulties inherent in extrapolation between preclinical and different phases of clinical evaluation are highlighted by our experience.

Haemodynamic effects have been observed with other antagonists of neuronal glutamate receptors such as aptiganel [10], selfotel [11] and CNS 5161 [14]. Potential complications of haemodynamic instability in the con-

text of acute cerebral infarction include haemorrhagic transformation or brain oedema following hypertensive responses and extension of cerebral infarction following hypotensive effects. No significant haemodynamic changes were noted in recipients of ZK 200775.

Conclusions

An observed reduction in levels of consciousness in dose group 2 was regarded as unsafe. After a conspicuous proportion of patients in dose group 3 experienced similar effects following a truncated infusion regime, a decision was made to terminate the study. No further clinical studies of ZK 200775 are planned.

Acknowledgements

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Appendix

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