Oxcarbazepine ([®]Trileptal) in Anti-epileptic Polytherapy

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Summary

The anti-epileptic activity of oxcarbazepine (OXC) was compared with that of carbamazepine (CBZ) and the primary active metabolite of OXC, a monohydroxy derivative (MHD). Altogether 255 patients receiving either OXC or MHD (192 and 63 patients respectively) were included in the analysis of efficacy. Out of these 255 patients a total of 40 were children. The duration of treatment varied between 8 and 24 weeks. The daily dose of OXC or MHD varied between 600 and 5400 mg (in children 600-2400 mg). Out of five studies two were double-blind controlled studies (including a total of 105 patients) whereas the remaining three were open studies.

The results of these studies indicate that, in adults with epilepsy, there is no statistically significant difference in overall seizure frequency between CBZ and OXC. In one double-blind study the number of generalized tonic-clonic seizures was significantly less frequent during treatment with OXC than with CBZ. No statistically significant difference with regard to side-effects was observed between OXC and CBZ.

The results in children with epilepsy show a statistically significant difference in seizure frequency in favour of OXC, in comparison with CBZ.

Overall, the polytherapy studies in adults and children support the effectiveness and safety of oxcarbazepine.

Introduction

[®]Trileptal, or oxcarbazepine (10,11-dihydro-10-oxo-carbamazepine) is a keto compound chemically related to carbamazepine. With carbamazepine it shares the dibenzazepine nucleus, but is structurally different in the 10,11-position. This molecular variation of oxcarbazepine results in a completely different metabolism compared with that of carbamazepine. The compound was synthesized as a follow-up compound for carbamazepine with a similar therapeutic profile but improved tolerability.

In animal models, oxcarbazepine displayed pronounced anticonvulsant activity comparable with that of carbamazepine in some tests and somewhat weaker activity in others (Baltzer and Schmutz, 1978; Schmutz *et al.*, 1986). The ED₅₀ value in rats and mice is about 10-20 mg/kg body weight after oral

administration. Like carbamazepine, oxcarbazepine is less active against chemically induced seizures. In animal models for focal seizures in man, oxcarbazepine showed complete seizure suppression at a single dose of 50 mg/kg body weight.

In addition, the tolerability of oxcarbazepine in animals was found to be superior to that of several established anti-epileptic compounds. The threshold dose for sedation in rats is about one-third of that seen after administration of oxcarbazepine.

In man, oxcarbazepine is metabolized very fast and almost completely to form the anti-epileptic active metabolite 10,11-dihydro-10-hydroxy-carbamazepine (Felmann *et al.*, 1978). As the metabolism of oxcarbazepine is very rapid and nearly total, all pharmacokinetics in the clinical development programme have been based on this monohydroxy derivative (MHD).

The clinical effect of oxcarbazepine in monotherapy has already been well documented (Reinikainen *et al.*, 1987; The Scandinavian Study Group, 1988). Altogether, of the 700 patients included in the clinical development programme with oxcarbazepine, 255 in five studies were receiving polytherapy. Two of these five studies were double-blind and included 105 patients. The comparison compound was either carbamazepine or MHD. The daily dose of oxcarbazepine was between 600 and 5400 mg/day, administered in a t.i.d. regimen. The duration of the polytherapy trials was between 8 and 24 weeks.

This review will concentrate on two polytherapy trials OT/EP4, and OT/EP7.

Polytherapy Trial OT/EP4

The trial designated OT/EP4 (Houtkooper *et al.*, 1987) included adult patients with unsatisfactory seizure control despite treatment with up to four anti-epileptic compounds. Forty-eight patients were included in this trial, which was designed as a double-blind cross-over study where patients were randomly allocated to either oxcarbazepine or carbamazepine, starting with doses of 300 mg oxcarbazepine and 200 mg carbamazepine. The doses were then individually titrated, in order to achieve optimum seizure control in each patient. After this titration the daily dose of oxcarbazepine or carbamazepine was kept constant for 12 weeks. The duration of the study was 24 weeks. According to the anti-epileptic profile of oxcarbazepine in animals, only patients with generalized tonic-clonic seizures and/or partial seizures with or without secondary generalization were included. The daily dose of concomitant anti-epileptic treatment was kept constant throughout the study. The mean daily dose of the trial medication was 2628 mg/day for oxcarbazepine and 1302 mg/day for carbamazepine.

Results

The mean number of seizures during the 12 weeks' treatment was 60.3 in the oxcarbazepine group, as compared with 66.0 in the carbamazepine group. Although a trend towards better seizure control was observed under oxcarbazepine, this difference did not attain statistical significance. A com-

parison of the mean number of tonic-clonic seizures (oxcarbazepine 8.2, carbamazepine 10.38), however, did reveal a statistically significant difference ($p < 0.05$) in favour of oxcarbazepine.

The tolerability of carbamazepine and oxcarbazepine was studied with regard to the number of patients experiencing side-effects, the nature of these side-effects, and the number of patients with abnormal laboratory findings during the treatment.

A total of 51% of the patients reported some kind of side-effect during treatment with oxcarbazepine, as compared with 42% of those on carbamazepine. This difference is not statistically significant.

No difference was observed between the two compounds with regard to the nature of the side-effects.

The laboratory findings showed some fluctuation in WBC count during both treatments, but these findings were not regarded as clinically relevant. However, the serum sodium concentration was observed to be lower during treatment with oxcarbazepine (135 mmol/l) than it was with carbamazepine (138 mmol/l), this difference being statistically significant ($p < 0.05$). This fall in serum sodium was always moderate and did not cause any patient to withdraw from the study.

The steady-state plasma concentrations of the concomitant medications were investigated during both treatment periods. During treatment with oxcarbazepine patients also receiving sodium valproate showed a statistically significant ($p = 0.004$) increase of 27% in the plasma concentration of this drug. Patients receiving both sodium valproate and phenytoin during treatment with oxcarbazepine showed similarly significant ($p < 0.001$) plasma concentration increases of 21% (sodium valproate) and 25% (phenytoin). The only reasonable explanation for this increase in the plasma concentration of concomitant medication is a reduced, or total absence of, oxcarbazepine enzyme induction potential with oxcarbazepine.

Polytherapy Trial OT/EP7

The second study, OT/EP7, was performed in children who showed unsatisfactory seizure control despite treatment with at least two anti-epileptic compounds, including carbamazepine. Only patients with generalized tonic-clonic and/or partial seizures with or without secondary generalization were included. Altogether 55 children were included in this study. The duration of treatment varied between 16 and 20 weeks. The study design was open and in all patients carbamazepine was replaced by oxcarbazepine at a 50% higher dose, whereas the concomitant anti-epileptic treatment was kept constant. The mean daily dose of oxcarbazepine was 1140 mg.

Results

A direct comparison between oxcarbazepine and carbamazepine with regard to the efficacy and tolerability parameters is not possible because of the design of the study. However, the number of seizures during the last month before entering the study was recorded in all patients.

The mean number of seizures per week was 11.0 during treatment with carbamazepine and 6.0 during treatment with oxcarbazepine. This difference is statistically significant ($p < 0.05$).

With regard to tolerability, a total of 36% of the patients experienced some kind of side-effect during treatment with oxcarbazepine. As far as the other studies both in monotherapy and in polytherapy are concerned, no difference was observed between oxcarbazepine and carbamazepine as regards the nature of the side-effects. One patient had to discontinue treatment because of excessive nausea and vomiting after 6 weeks' therapy with oxcarbazepine in a daily dose of 1200 mg. Extensive screening of laboratory values, including WBC counts and liver-function parameters, did not result in any clinically relevant findings during treatment with oxcarbazepine.

Conclusion

In the light of the results obtained in monotherapy, the results of the polytherapy studies can be seen as further evidence in support of the efficacy and tolerability of oxcarbazepine. The findings of these polytherapy trials show that:

oxcarbazepine has an efficacy profile comparable to that of carbamazepine in patients receiving polytherapy,
the tolerability of oxcarbazepine is equal to that of carbamazepine in patients receiving polytherapy, and
the capacity of oxcarbazepine for enzyme induction is significantly less compared with that of carbamazepine.

All in all, oxcarbazepine can be regarded as a viable alternative to carbamazepine with regard to efficacy in patients receiving polytherapy. In addition, the lower capacity of oxcarbazepine for enzyme induction makes the management of polytherapy easier, as compared with carbamazepine.

References

- Baltzer, V. and Schmutz, M. (1978). Experimental anticonvulsive properties of GP 47 680 and of GP 47 779, its main human metabolite; compounds related to carbamazepine. *In* "Advances in Epileptology - 1977." (Eds H. Meinardi and A.J. Rowan), pp. 295-299. Swets and Zeitlinger, Lisse, Amsterdam.
- Feldmann, K.F., Brechbühler, S., Faigle, J.W. and Imhof, P. (1978). Pharmacokinetics and metabolism of GP 47 680, a compound related to carbamazepine in animals and man. *In* "Advances in Epileptology - 1977." (Eds H. Meinardi and A.J. Rowan), pp. 290-294. Swets and Zeitlinger, Lisse, Amsterdam.
- Houtkooper, M.A., Lammertsma, A., Meyer, J.W.A., Goedhart, D.M., Meinardi, H., van Oorschot, C.A.E.H., Blom, G.F., Höpener, R. J. E. A. and Hulsman, J.A.R.J. (1987). Oxcarbazepine (GP 47 680): a possible alternative to carbamazepine? *Epilepsia*, **28**, 693-698.
- Reinikainen, K.J., Keraanen, T., Halonen, T., Komulainen, H. and Riekkinen, P.J. (1987). Comparison of oxcarbazepine and carbamazepine: a double-blind study. *Epilepsy Research*, **1**, 284-289.
- Schmutz, M., David, J., Grewal, R.S., Bernasconi, R. and Baltzer, V. (1986). Pharmacological and neurochemical aspects of tolerance. *In* "Tolerance to Beneficial and Adverse Effects of Antiepileptic Drugs." (Eds H. Frey *et al.*), pp. 25-34. Raven Press, New York.
- The Scandinavian Oxcarbazepine Study Group (Running committee: Dam, M., Ekberg, R.,

Läyning, Y., Waltimo, O. and Jakobsen, K.) (1988) A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Research*, 3, 70-76.