Clinical evaluation of carbocyclic oxetanocin G eyedrops in the treatment of herpes simplex corneal ulcers

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Abstract

Background—Acyclovir (ACV) ophthalmic ointment is effective in the treatment of herpetic keratitis. However, when applied, the ointment has an unpleasant feeling and some cases are resistant to ACV. A new antiviral compound, carbocyclic oxetanocin G (C.OXT-G) has potent anti-herpes simplex virus activity and high water solubility, so the clinical effect of C.OXT-G eyedrops on ulcerative herpetic keratitis was evaluated.

Methods—Studies were conducted on the corneal ulcers in 37 eyes of 27 patients. Patients with typical dendritic or geographic corneal ulcers were treated with 0.1% C.OXT-G eyedrops, applied five times a day, together with eyedrops of an antibiotic applied four times a day. The eyes were examined at least twice a week until the ulcers healed, and thereafter at intervals for up to 3 months.

Results—All of the ulcers healed, their average healing time being 4.9 (SD 2.2) (range 2 to 9) days. The ulcers in 20 of the 37 eyes were induced by the use of corticosteroid or immunosuppressive drugs, and their average healing time was 4.8 (2.3) days. No adverse drug reactions were seen during the observation period in this trial.

Conclusion—Eyedrops containing 0.1% C.OXT-G are excellent and safe for treatment of herpes simplex corneal ulcers in humans.

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but the ointment has an unpleasant feeling when applied. Therefore, we have been searching for new anti-herpes simplex virus (HSV) drugs that are soluble in water and have potent anti-HSV activity.

Carbocyclic oxetanocin G (C.OXT-G) is a new antiviral compound in which guanine is attached to a cyclobutane ring (Fig 1).¹¹ It is active against not only HSV,^{11–13} but also other viruses including varicella zoster virus,^{11 13} cytomegalovirus,^{11–13} Epstein Barr virus,¹³ and human immunodeficiency virus.^{13 14} It seems to be phosphorylated by thymidine kinase (TK) to C.OXT-G monophosphate and finally to its triphosphate form, which may inhibit DNA polymerase.^{15–17} However, it may have some other mode of activation beside phosphorylation by TK, since it is active against cytomegalovirus, which is TK negative. We found that this compound, C.OXT-G, is a possible candidate for use as eyedrops in treatment of herpetic keratitis because as eyedrops it exhibited an excellent therapeutic effect in the treatment of herpetic keratitis in rabbits and had no side effects.¹⁸ This paper describes the clinical evaluation of C.OXT-G eyedrops for the treatment of herpes simplex corneal ulcers.

Materials and methods

Studies were made on patients with typical dendritic or geographic corneal ulcers who visited Tokushima University Hospital. The diagnosis of herpes simplex corneal ulcers was made on the basis of the clinical presence of typical

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5-Iodo-2'-deoxyuridine (IDU) was the first drug found to be clinically effective in the treatment of herpetic keratitis.¹ However, owing to its cytotoxicity it can be used only topically as eyedrops or ointment, not systemically. Acyclovir (ACV) overcomes the limitation of IDU because it can be used not only topically as an ointment, but also systemically owing to its specific mode of action and low toxicity.^{2 3} IDU and ACV are commercially available for treatment of herpetic keratitis in Japan. There are also other drugs for treatment of herpetic keratitis, such as adenine arabinoside (ara-A)⁴ and trifluorothymidine (F₃T),⁵ which are marketed in Europe and the USA. However, these drugs also have some cytotoxicity, although less than that of IDU. Owing to its better therapeutic effect,^{6–8} lower toxicity,⁹ and better penetration into the anterior chamber¹⁰ than IDU, ACV is now the drug of choice in the treatment of herpetic keratitis in Japan,

Figure 1 Structure of carbocyclic oxetanocin G.

dendritic or geographic ulcers. Also when possible, a very small part of the ulcer edge was scraped off and a fluorescent antibody test against HSV was made for confirmation of the diagnosis. Informed consent was obtained from all patients included in this study.

Treatment was carried out on an outpatient basis. Eyedrops of 0.1% C.OXT-G, which was synthesised by one of the authors (TM), were made by dissolving the compound in physiological saline without a preservative and sterilising the solution of pH 6.6 by filtration. Patients were told to apply exactly one drop (0.051 ml) of 0.1% C.OXT-G eyedrop solution five times a day during the time when they were awake. In addition, they were told to apply one drop of antibiotic eyedrop solution, usually 0.3% ofloxacin, four times a day to prevent secondary bacterial infection. If the patients were suffering from iritis at the start of this study, they also applied a drop of 1% atropine eyedrop solution once a day. The patients were advised not to apply other eyedrops at the same time. If the patients were using steroid eyedrops and stromal involvement was not seen or was minimal, they stopped applying the steroid drops and followed the above treatment schedule during this trial. However, if the patients were using steroid eyedrops and stromal involvement or iritis was prominent, they were weaned off by decreasing the steroid concentration in a way such as that described by McGill and others¹⁹ during the above treatment schedule. If the patients were taking immunosuppressive drugs systemically because of other diseases, they continued their use in addition to applying the above topical treatment during the trial.

The patients' eyes were examined at least twice a week using a photo slit-lamp after staining with fluorescein until the ulcers had healed, then once every 7 days for 1 month, and 1 and 2 months later. Thus they were followed up for 3 months after the disappearance of ulcers. The end point of ulcer healing was judged by the same criterion as that used by others^{18,20}; namely, we judged ulcers as healed when specific fluorescein staining of the sites of the ulcers disappeared. We disregarded fine microscopic punctate stainings of the epithelial surface, if any, when judging the healing time. C.OXT-G eyedrops were applied five times a day until 1 week after the ulcers had healed. Application of the drops was then stopped, or continued three times a day for another week if there was still a granular appearance at the sites of previous ulcers.

At each visit to hospital, the patients were examined by more than one ophthalmologist to obtain consistent agreement on whether ulcers had healed, and photographs were taken with a Zeiss photo slit-lamp. The cornea, the lids, and the conjunctiva were all examined for possible adverse drug reactions during the whole observation period.

Results

Studies were made on the corneal ulcers in 37 eyes of 27 patients (14 male, 13 female;

Table 1 Effects of 0.1% carbocyclic oxetanocin G eyedrops on herpes simplex corneal ulcers

Cases: 37 eyes (27 patients; male 14, female 13)
No of eyes healed: 37 (100%)
Healing time: 4.9 (SD 2.2) days (range, 2–9 days)
Dendritic ulcers (32 eyes): 4.7 (2.1) days
Geographic ulcers (5 eyes): 6.2 (2.3) days
Ulcers induced by immunosuppressive drugs: 20 eyes (11 patients*)
Healing time: 4.8 (2.3) days

*One patient had had a kidney transplantation and suffered nine ulcer recurrences.

average age 56.9 years). All these ulcers healed, their average healing time being 4.9 (SD 2.2) days (range 2 to 9 days). Of the 37 eyes, 32 had dendritic ulcers whose average healing time was 4.7 (2.1) days, while the other five had geographic ulcers which showed an average healing time of 6.2 (2.3) days. The ulcers in 20 eyes of 11 patients were induced by the use of corticosteroid eyedrops (10 eyes) or systemic immunosuppressive drugs (10 eyes). However, the ulcers in these eyes all healed with an average healing time of 4.8 (2.3) days. One of the 11 patients was a man aged 58 years on his initial visit who had had a kidney transplantation and had to take immunosuppressive drugs, mainly cyclosporin A. He had suffered from ulcerative herpetic keratitis nine times in the past 3 years. However, his corneal ulcers were always healed by 0.1% C.OXT-G eyedrops. The average healing time of ulcers in this patient was 5.2 (2.3) days. Our results are summarised in Table 1.

No adverse drug reactions were seen during the observation period in this trial.

Discussion

IDU and ACV are the only drugs commercially available in Japan for the treatment of herpetic keratitis. ACV has a better therapeutic effect,^{6–8} less toxicity,⁹ and better penetration into the anterior chamber¹⁰ than IDU, so use of ACV ophthalmic ointment is now the treatment of choice in Japan. However, the ointment has an unpleasant feel and some cases are resistant to ACV.^{21–24} The anti-HSV drugs ara-A⁴ and F₃T⁵ are also effective for the treatment of herpetic keratitis. But ara-A must be used as an ointment, which also has an unpleasant feel when applied, and for various reasons, no pharmaceutical companies market F₃T eyedrops in Japan. Therefore, new anti-HSV drugs with strong anti-HSV activity and high water solubility are required for preparation of effective eyedrops.

We found in previous studies that C.OXT-G is a possible candidate, because 0.1% C.OXT-G eyedrops applied 10 times a day exhibited an excellent therapeutic effect in the treatment of herpetic keratitis in rabbits.¹⁸ Moreover, no toxic effects of C.OXT-G eyedrops were detected during these animal experiments, and after application of 0.1% C.OXT-G eyedrops five times a day for 3 months to six normal rabbits, the corneas did not show any abnormalities on slit-lamp or histopathological examination.

Based on these findings of the efficacy and safety of 0.1% C.OXT-G eyedrops against herpetic keratitis in rabbits, in the present clinical trial, 0.1% C.OXT-G eyedrops were applied five times a day to typical herpes simplex corneal ulcers. Results showed that 0.1% C.OXT-G eyedrops were very effective for the treatment of herpes simplex corneal ulcers in humans. Our preliminary results with the smaller number of seven eyes were reported in Japanese elsewhere,¹⁸ and to the best of our knowledge, this is the first report in English of a large scale study showing the efficacy of C.OXT-G against herpetic keratitis in humans. The ulcers in 20 eyes were induced by the use of steroid eyedrops or systemic immunosuppressive drugs, but all healed on treatment with C.OXT-G eyedrops. Thus, unlike IDU,²⁵ this compound was effective against steroid induced herpes simplex corneal ulcers in all the patients studied. One patient was receiving immunosuppressive drugs continuously after kidney transplantation, and suffered from ulcerative herpetic keratitis nine times in 3 years, but each time the keratitis soon healed on treatment with C.OXT-G. This indicates that the compound is therapeutically effective, but cannot prevent recurrence of this disease.

Kaufman and his associates first examined IDU eyedrops on the same disease using the same criterion of ulcer healing as ours and obtained average healing times of 2.9 days for dendritic ulcers without stromal involvement (33 cases), 5.8 days for dendritic ulcers with stromal involvement (42 cases), and 6.5 days for very large geographic ulcers (12 cases).¹ McGill and his associates reported ulcer healing in an average of 4.5 days on ACV treatment (28 cases) compared with 6.2 days on ara-A treatment (29 cases).¹⁹ Kitano and others also carried out a double blind comparative study of ACV and IDU on herpes simplex corneal ulcers. They observed ulcer healing in an average of 5.70 days on ACV treatment (50 cases) compared with 6.93 days on IDU treatment (43 cases).⁸ There are many other similar studies showing that with a compound that is effective for the treatment of ulcerative herpetic keratitis, the average time of ulcer healing is about 7 days or less. Although our study was an open trial and did not have a proper blind control, we can roughly estimate the efficacy of C.OXT-G by comparing the healing time with those in other reports, since the trial was done on typical dendritic or geographic corneal ulcers and the efficacy was evaluated in the same way by the healing time. Our results showed the efficacy of C.OXT-G with no adverse reactions in humans. This trial was an open study, not a double blind controlled study, but this was essential as a first step in testing a new therapy¹ and our results indicated the need for further studies. The next step in the evaluation of C.OXT-G should be double

blind controlled clinical studies using 0.1% C.OXT-G and 0.1% IDU or 1% F₃T eyedrops.

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