Carbomer and Sodium Hyaluronate Eyedrops for Moderate Dry Eye Treatment

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ABSTRACT

Purpose. This randomized, double-masked study compared the effectiveness of two commercially available ocular lubricants containing either 0.3% Carbomer 934 or 0.18% sodium hyaluronate (SH) in treating moderate dry eye.

Methods. Sixty-five subjects with dry eye were recruited and supplied with eyedrops containing either Carbomer or SH to use for a month. Principle outcome measures were the severity of symptoms of ocular irritation, tear break-up time without (NIBUT) and with (TBUT) fluorescein, and corneal and conjunctival staining with fluorescein and lissamine green, respectively. At the end of the experiment, subjects were also asked, on average, how many times a day they used the treatment and the duration of any postinstillation blur.

Results. Both Carbomer and SH reduced the symptom severity and ocular surface staining, but neither had a lasting effect on NIBUT or TBUT. The treatment effects of Carbomer and SH were equivalent for symptoms, NIBUT and TBUT. However, for both corneal and conjunctival staining, SH outperformed Carbomer in improving the integrity of the ocular surface. There was no difference in the average instillation frequency of the two products. Visual disturbance after instillation of either formulation was generally short, but lengthy periods of blur were significantly more common after the use of Carbomer.

Conclusions. Both of the eyedrops trialled are suitable for patients with moderate dry eye, but of the two, the SH-containing treatment has marginal benefits in therapeutic efficacy and has less propensity to cause visual disturbance.

Optom Vis Sci 2008;85:750–757

Key Words: artificial tears, carbomer, dry eye, ocular comfort index, ocular lubricants, sodium hyaluronate, tear substitutes

Tear substitutes increase the volume of fluid at the ocular surface, and in doing so reduce cellular damage by lessening the osmotic pressure of the tear film and friction from eyelid movements in dry eye. The majority of available formulations do not actively modulate inflammation, however, their dilution of pro-inflammatory substances is likely beneficial. These treatments are frequently effective in mild and moderate dry eye by interrupting its deleterious self-sustaining cycle, although the resolution of symptoms and objective signs is often incomplete.1–3 For the foreseeable future, tear substitutes will likely continue to be the most common initial therapeutic strategy for this group of conditions, owing to their simplicity and low cost. Appropriate dosing of these products is determined by disease severity and the length of time that they remain at the ocular surface, an attribute primarily dependent on their viscosity.4 Eyedrops containing Carbomers or sodium hyaluronate (SH) are increasingly being used because of their non-Newtonian time-dependent response to shear strain. This causes the viscosity of these substances to reduce with agitation. These treatments therefore have a longer ocular residence time over more watery formulations and so permit more convenient dosing without impeding blinking or causing the marked visual blur associated with petrolatum-based ointments.5

Structurally, the Carbomer resins (–910, –934, –940, –941, and –962) are synthetic, high molecular weight, nonlinear polymers of predominantly acrylic acid, cross-linked with a polyalkenyl polyether. The listed formulations are chemically similar to each other but differ in ascending molecular weight. These anionic polymers expand on neutralization in aqueous media to form three-dimensional
gel networks. SH is a glycosaminoglycan disaccharide biopolymer that in solution forms entangled chains linked by noncovalent interactions. Moreover, SH has a huge capacity to bind water, 1000-fold its own weight, and resists dehydration. Long considered an inert filling material of the extracellular matrix, SH is now recognized as having an important role in cellular migration and immunomodulation. The specific rheological characteristics of both Carbomer and SH are dependent on their molecular size and concentration, and are influenced by the pH and ionic charge of their environment; although pH has little appreciable effect on either Carbomers or SH within the physiological range.

This study compared the effectiveness of two eyedrops containing either 0.3% Carbomer 934 or 0.18% SH in treating moderate dry eye over a month.

METHODS

Subjects

Sixty-five subjects (median 38 years, ranging between 21 and 64 years) with moderate dry eye were recruited from students and patients attending primary care clinics at Cardiff University (Cardiff, UK). The tenets of the Declaration of Helsinki were followed. Informed consent was obtained and the study was approved by the School of Optometry and Vision Sciences' research ethics committee. Moderate dry eye was defined as tear-break-up time after fluorescein instillation (TBUT) <10 s, staining of the cornea with fluorescein and bulbar conjunctiva with lissamine green between grades 1 and 3 with the logarithmic Oxford scheme. All of these signs had to be present in both eyes and after a run-in period of 7 to 14 days, wherein they were instructed to use unpreserved 0.9% saline (Unilarm; CIBA Vision Ophthalmics, Annonyay, France), as required, up to four times a day in both eyes. Other topical eyedrops were prohibited during this week.

Experimental Design

After the initial screening appointment and run-in period, baseline measurements were obtained: symptom severity, tear break-up time, and ocular surface staining. Subjects were then supplied with preservative-free monodoses of either 0.3% Carbomer 934 (Lacryvix; Alcon, Hüningen, Switzerland) (n = 33) or 0.18% SH (Vismed; TRB Chemedica AG, Munich, Germany) (n = 32). These were relabeled to give them a very similar appearance, and were allocated in a double-masked manner using block randomization to ensure nearly equal group numbers. Baseline data for the two groups is presented in Table 1.

Instructions were given to use the tear substitutes as symptoms dictated with a minimum of two and maximum of eight instillations in both eyes, every day for 28 ± 3 days. After the month of eyedrop use, subjects returned for a final visit where assessment of symptoms and objective testing was repeated.

Subjects were asked to refrain from using treatments for at least 4 h before every visit. For each subject, all measurements were taken in one randomly selected eye, and the same eye was used during testing at the baseline and final visits.

The severity of symptoms, taken here to represent an aggregate function of how often symptoms occur and how intense they are when they do, was investigated with the ocular comfort index (OCI). This is a psychometrically validated 12-item instrument with significant advantages over other existing questionnaires that attempt to quantify this variable. The OCI consists of six question doubles that inquire about the frequency and intensity of dryness, grittiness, stinging, pain, and itching of the eyes in the last week. It uses a seven-category (0 to 6) rating scale, but does not simply summate these ratings to derive an ordinal ranking. Through a variant of item-response theory known as Rasch analysis, it transforms these raw data counts into estimates of personal ability on a linear interval scale and is thus better able to quantify change. This scale runs from 0 to 100 abstract units. Furthermore, the scoring technique is based on probability and uses statistical methods to account for missing data more satisfactorily than traditionally scored questionnaires. The vernacular of Rasch analysis is a relic from its origins in the educational testing of aptitude, where persons with more ability are more likely to score higher than those with lower abilities, and the term has nothing to do the capability of respondents to complete the questionnaire. The questions of the OCI are negatively worded, and therefore, contrary to the intuition of most clinicians, with this instrument more “able” persons experience a greater degree of discomfort. It follows that individuals with severe symptoms will score highly with the OCI. The theory of Rasch analysis has recently been reviewed.

Tear break-up time was assessed without (NIBUT) and then with (TBUT) fluorescein. NIBUT was measured using the Tearscope Plus (Keeler Limited, Windsor, UK). This apparatus consists of a circular cold light source that projects a grid onto the tear film, which acts as a convex mirror, forming an image that can be visualized with a slitlamp. The time elapsing from a blink to the first detectable distortion of the grid’s image is the NIBUT. To evaluate TBUT, 1 μl of 2% fluorescein (Minims; Chauvin Pharmaceuticals, Romford, Essex, UK) was instilled onto the temporal bulbar conjunctiva with the subject looking superior-nasally.

During measurement, the tear film was viewed with a slitlamp and the cornea was illuminated obliquely by a circular beam, 10 mm in diameter and 30° temporal to the observation system. The maximum diameter permitted by the slitlamp was used to minimize scanning and the potential for delay in the detection of tear-rupture. Visualization of tear film fluorescence was enhanced with a cobalt blue filter transmitting 330 to 400 nm over the

| Table 1. Baseline data for the two treatment groups supplied with eyedrops containing either Carbomer or sodium hyaluronate (SH) |
|-----------------|----------------|----------------|
| Group variable  | Carbomer | SH | Total |
| Number of subjects | 33      | 32  | 65    |
| Median age      | 36 yr   | 39 yr | 38 yr |
| Mean OCI score  | 44.0 units | 42.5 units | 43.3 units |
| Median NIBUT    | 4.4 s   | 5.7 s | 5.1 s |
| Median TBUT     | 3.4 s   | 4.7 s | 4.3 s |
| Median corneal staining | 1.5 log units | 1.6 log units | 1.6 log units |
| Median conjunctival staining | 2.1 log units | 2.4 log units | 2.2 log units |
illuminator system, an ancillary part of the slitlamp, and a gelatin filter transmitting >510 nm over the microscope's objective lens (Kodak Wratten #12; Rochester, NY). With both break-up time methods, the median of three recordings was used for analysis. The median was chosen because it is insensitive to outliers, for which these measures are prone.

After assessment of tear break-up time, fluorescein and lissamine green were used to assess the integrity of the corneal and bulbar conjunctival surfaces, respectively. The fluorescein (Fluoret; Chauvin Pharmaceuticals, Romford, UK) and lissamine green (Lissamine Green Ophthalmic Strips; Rose Stone Enterprises, Alt Loma, CA) impregnated strips were soaked in saline and applied to the inferior conjunctiva. The extent of staining was evaluated with the logarithmic Oxford scheme. With this reference scale, staining was recorded in log units (log10 of the dot count), rather than arbitrary grades, rounding to the nearest half log unit. The nasal and temporal bulbar conjunctiva were scored separately and then summed.

At the end of the experiment, subjects were asked, on average, how many times a day they used the treatment and, rounded to the nearest whole minute, the duration of any postinstillation blur.

Details of Carbomer and SH Treatments

Carbomer 934 is reported to be a polymer of acrylic acid crosslinked with alkyl-succrose, although the exact composition of the Carbomer polymers is proprietary information. The treatment containing Carbomer used in this study had a pH of 7.5, was preservative-free, and was marketed as isotonic to normal tears.

The treatment containing SH acquired this substance by bacterial fermentation with a restricted molecular weight, averaging 1.2 × 10^6 Da. It was formulated to have a pH of 7.4 and was relatively hypotonic (150 mOsm/l) to normal tears. It also contained trace quantities of various ions, but no preservatives (Table 2).

Statistics

Continuous Data. The treatment effect was found for the OCI score, NIBUT and TBUT by subtracting the value at the end of the study from that obtained at baseline, immediately before tear substitutes were issued. The distribution of break-up time was skewed in the sample, as has been reported previously. However, the distribution of treatment effects for both NIBUT and TBUT was compatible with a normal distribution, and so parametric tests were appropriate for this difference data. Confidence intervals (CIs) for the treatment effect of both products were calculated, and a one-sample t-test was used to test the null hypothesis that the average treatment effect of each was zero. Differences between the treatment effects of the two products were compared with CIs and t-tests for two independent groups.

Rejection of the null hypothesis, or a CI for group differences that does not include zero, is statistical evidence of disparity between group averages, but the converse is not positive evidence for equivalence. Statistical equivalence between group averages can, however, be established if the entire length of the CI for the difference lies within an amount that is considered inconsequential. Other situations should be considered statistically indeterminate. The size of the difference between groups that is considered trivial is not a statistical problem, but a semi-arbitrary choice. Values selected in this work were those deemed by the investigators to be the smallest amount that may influence a clinical decision in the diagnosis or management of dry eye. This choice was based on their personal experience, rather than universally accepted criteria. These threshold values are listed in Table 3.

Grouped Data. The Oxford grading scheme has a logarithmic structure. It therefore derives structured numerical data, rather than unstructured ordinal data, because there is a mathematical relation between the scores on its scale. Although not obligatory, it is commonly used in a discreet manner, rounding to the nearest half log unit, and this was the recording procedure used in this work. When the number of category groupings greatly exceeds the range encountered in the sample, minimal error is incurred by simplifying the statistical analysis of data by assuming it to represent a continuous variable. This has the advantage of enabling parametric tests to be considered. However, when, as in this case, there are only a few categories, such treatment is inappropriate.

There are statistical techniques that account for grouping within data without losing information by ignoring its algebraic structure, but here an additional consideration was that the distribution of the treatment differences of the ocular surface staining data was skewed, with no difference being noted more frequently than the normal distribution would predict. Accordingly, the most suitable hypothesis analyses were rank-based, which, in addition to not making distributional assumptions, are intrinsically bleue to the discrete or continuous nature of data. Specifically, the Wilcoxon matched pairs signed rank sum test was used to compare scores before and after topical therapy, and the Mann-Whitney test was used to compare the treatment effects of the two parallel study.

### TABLE 2.

Excipients of the two eyedrops used in this work

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Concentration (mg/ml)</th>
<th>Ingredient</th>
<th>Concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>50</td>
<td>Disodium monohydrogen phosphate</td>
<td>3.22</td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>Sodium chloride</td>
<td>2.79</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>1.25</td>
<td>Potassium chloride</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Magnesium chloride</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium chloride</td>
<td>0.089</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sodium citrate</td>
<td>0.26</td>
</tr>
</tbody>
</table>

### TABLE 3.

Changes in principle outcome measures that were considered clinically significant

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Clinically significant change</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCI score</td>
<td>3 units</td>
</tr>
<tr>
<td>NIBUT</td>
<td>3 s</td>
</tr>
<tr>
<td>TBUT</td>
<td>3 s</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>0.5 log units</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>0.5 log units</td>
</tr>
</tbody>
</table>

Optometry and Vision Science, Vol. 85, No. 8, August 2008
TABLE 4.
The effect of treatments containing either carbomer or sodium hyaluronate (SH) after 1 month of use in subjects with dry eye

<table>
<thead>
<tr>
<th>Treatment effect: Post-treatment value minus baseline (95% CI or median)</th>
<th>Difference in effect: Carbomer minus SH (95% CI or difference in medians)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbomer</td>
<td>SH</td>
</tr>
<tr>
<td>OCI symptoms</td>
<td>-5.1 to -8.5 units</td>
</tr>
<tr>
<td>TIBUT</td>
<td>-0.09 to 0.87 s</td>
</tr>
<tr>
<td>NIBUT</td>
<td>-0.33 to 1.16 s</td>
</tr>
<tr>
<td>Corneal staining</td>
<td>-0.44 log units</td>
</tr>
<tr>
<td>Conjunctival staining</td>
<td>-0.42 log units</td>
</tr>
</tbody>
</table>

The differences between the treatment effects of these two eyedrops are listed in the right-hand column of the table as the treatment effect of carbomer minus the treatment effect of SH.

Differences are generalized with confidence intervals (CIs) for parametric data, otherwise average values are presented. Statistically significant differences are indicated by lowercase superscript alphabet.

arms, both with corrections for tied ranks. Unfortunately, the estimation of effect size with CIs is not possible with either of these analyses.

The median was used as an estimate of central tendency for skewed grouped data. When the middle rank was contained in a group with a frequency exceeding one, rather than use the midpoint of the category’s range, a more exact value was obtained by interpolation. In this method, the fraction of the range of the group containing the 50th percentile, corresponding to the middle rank minus the cumulative frequency of the preceding lower rank, relative to the frequency of the group containing the middle value, was taken as the median.28

A p-value of <0.05 was interpreted as statistically significant in all hypothesis tests.

RESULTS

A summary of results is presented in Table 4. Both the Carbomer and SH treatments trialed reduced symptom severity and ocular surface staining (p < 0.01; one sample t-tests) (Figs. 1 and 2). In contrast, visual symptoms and SH did not statistically change from baseline after the use of either eyedrop (Fig. 3).

For the improvement in the OCI score, not only was this change statistically significant but also the lowest values of the 95% CIs for the treatment effect of both eyedrops exceed the minimal clinically important difference chosen before analysis. It can therefore be confidently inferred that the two treatments bring about a meaningful improvement in symptoms. The skewed distribution of the treatment effect data for corneal and conjunctival staining meant that a similar analysis with CIs could not be undertaken for these outcome measures.

The treatment effects of the Carbomer and SH products were compared directly. No statistically significant difference was found between their beneficial effect on symptoms (p = 0.94; t-test for independent groups). Furthermore, the 95% CI for the difference in their treatment effects on the OCI score did not include a value that exceeded the threshold chosen to signify a clinically important difference. This provides evidence that the two treatments should be considered clinically equivalent in their capacity to reduce symptoms. In contrast, there was a small, but statistically significant, difference in their ability to improve ocular surface health. The treatment containing SH reduced corneal and conjunctival staining more than the Carbomer formulation (p = 0.036 and 0.012, respectively; t-tests for independent groups).

There was no statistically significant difference between the self-reported instillation frequency of the two treatments (p = 0.20; Mann-Whitney test) (Fig. 4A). The median number of drops instilled per day for the two treatments were 2.1 and 2.3 for Carbomer and SH, respectively.

The duration of visual disturbance after drop instillation was typically reported to be less than 1 min with both treatments, (16/33) 48% and (2/32) 6% experienced blur for 1 min or

FIGURE 1.
The treatment effect of eyedrops containing either Carbomer or SH on the OCI score. A negative number indicates a reduction in the severity of symptoms from baseline after treatment. In the box-plot, the box size delineates the 25th and 75th percentiles, and its whiskers indicate the extreme values that are closer than one and a half box lengths from the box; more extreme values are considered outliers and are denoted by an open circle.
FIGURE 2.
The treatment effect of eyedrops containing either Carbomer or SH on corneal staining (A) and conjunctival staining (B), assessed with the logarithmic Oxford scheme. A negative number indicates a reduction in the amount of ocular surface staining after treatment. In the box-plot, the box size delineates the 25th and 75th percentiles, and its whiskers indicate the extreme values that are closer than one and a half box lengths from the box; more extreme values are considered outliers and are denoted by an open circle.

FIGURE 3.
The treatment effect of eyedrops containing either Carbomer or SH on non-invasive break-up time (NIBUT) (A) and break-up time after fluorescein instillation (TBUT) (B). A positive number indicates a lengthening of break-up time from baseline after treatment. In the box-plot, the box size delineates the 25th and 75th percentiles, and its whiskers indicate the extreme values that are closer than one and a half box lengths from the box; more extreme values are considered outliers and are denoted by an open circle.

longer with Carbomer and SH, respectively, which gives a relative risk of 7.8 (p < 0.01; Fisher exact test) (Fig. 4B). However, it should be noted that, even when present, blur was seldom regarded as debilitating with either treatment.

DISCUSSION

Both Carbomer and SH reduced the severity of symptoms and ocular surface staining after a month of use, supporting their inclusion in eyedrops supplied to manage dry eye. The benefits reported in this work agree with the majority of previous studies that have examined the effectiveness of eyedrops containing these ingredients.29–37

In contradistinction, neither Carbomer or SH were found to have a statistically significant effect on NIBUT or TBUT. It is possible that the results for break-up time may have been type II errors (false negatives or β errors) because of a large variability in these measurements. A poor test-retest repeatability has previously been reported for break-up time.38 However, in this case, the 95% CIs for treatment effect do not include the value that was chosen as the threshold for clinical importance, and therefore, we can be
confident that a clinically important treatment effect was not missed. The lack of treatment effect on break-up time is accounted for by the fact that the usage of eyedrops was not allowed in the 4 h preceding measurement, and so almost no lubricant would have been at the ocular surface during assessment. It follows that the use of these products does not permanently improve the tear film, but only brings about a temporary change to its rheology and function. Repeated dosing throughout the day and ongoing therapy are thus required.

The treatment effects of Carbomer and SH were equivalent for symptom severity, NIBUT and TBUT. However, for both corneal and conjunctival staining, SH outperformed Carbomer in improving the integrity of the ocular surface. This latter result is despite the longer ocular residence time of Carbomer vs. SH reported in the literature and the lack of any differential in dosing load. Using quantitative gamma scintigraphy, the estimated half-life of 0.2% SH on the ocular surface has been predicted to be just under five and a half minutes, which is significantly less than about 15 min for Carbomer 940, a value estimated from data published by Wilson et al. An explanation of this apparent incongruity may be the result of SH performing better than Carbomer at low concentrations. Alternatively, it may reflect the role of the former in promoting epithelial migration and, at least at certain molecular weights, its anti-inflammatory properties. Through these mechanisms, SH could augment wound healing of the compromised ocular surface in dry eye and encourage its robustness to further insult. These non-lubricating effects of SH are thought to be mediated by cell surface receptors. Three of these receptors have been molecularly characterized, namely cluster of differentiation antigen (CD)-44, receptor for hyaluronate-mediated motility (RHAMM) and intercellular adhesion molecule (ICAM)-1, and notably CD44 has been identified at the ocular surface. Additionally, there is some evidence that Carbomer formulations, both with and without preservatives, can produce in vitro toxic effects to corneal cells, which is not the case for SH. However, although statistically significant, the difference in the ability of the treatments to reduce corneal and conjunctival staining was relatively small. The difference in treatment effect of the two formulations for both these outcome measures was typically only 0.5 log units, which is at the threshold of clinical importance. It is also uncertain if the therapeutic effects of Carbomer were just delayed compared to SH, and would have led to an equivalent improvement in ocular surface health if the treatment period had been extended.

It is interesting that, given reports in the literature which suggest SH drains more rapidly from the eye than Carbomer, eyedrops containing SH were not instilled more frequently. This may have been because, as suggested above, this treatment retained its effectiveness at lower concentrations than those including Carbomer. Alternatively, it may have reflected a reluctance to dose more often because of the associated inconvenience or, perhaps, inaccuracies in subject recall.

The duration of visual disturbance after drop instillation rarely lasted longer than 1 min for SH, but was not uncommon with Carbomer, although it was generally not considered debilitating. Lengthy periods of blur after the use of Carbomer have been noted in previous clinical trials but not after the use of SH. By rubbing the treatments used in this study between one fingers, it could be crudely discerned that the eyedrop containing Carbomer was more viscous than the SH formulation. The increased viscosity of Carbomer would have likely delayed its mixing with tears after instillation and may have accounted for this subjective difference.

The treatment containing SH was hypotonic with normal tears, whereas that containing Carbomer was isotonic. It should also be considered that this difference in osmolarity may have affected their efficacy. Elevated tear osmolarity is recognized as a feature common to all subtypes of dry eye and has been shown to initiate inflammation in adjacent epithelium. Moreover, it has been reported that after 90 days of using a hypotonic formulation of SH, subjects with Sjögren syndrome had significantly improved ocular surface epithelial health, in terms of staining with fluorescein and Rose Bengal, and impression cytology, vs. an isotonic comparative. However, contradictory results have been reported by
others who reasoned that the osmolarity of eyedrops has little influence on their effectiveness because their reductions in tear osmolarity are of a short duration and, relative to the tear film in dry eye, even formulations isotonic with normal tears are hypotonic. These opposing results may have resulted from differences in dry eye severity in subject samples, outcome measures assessed, and differences in the osmolarity of treatments. On balance, it seems that the lower osmolarity of the eyedrop containing SH would have likely enhanced its effectiveness, although its relative importance is uncertain.

CONCLUSIONS

This study found that the two commercial eyedrops tested, containing 0.3% Carbomer 934 or 0.18% SH, reduced the severity of symptoms and extent of ocular surface irritation in subjects with moderate dry eye after use for a month, but neither had a lasting effect on tear film stability. The effectiveness of these treatments on subjective and objective markers was similar, although SH was slightly superior to Carbomer in attaining an improvement in the integrity of the corneal and conjunctival epithelium. Both the eyedrops trialed are suitable for patients with moderate dry eye, but of the two, the SH-containing treatment has marginal benefits in terms of therapeutic efficacy and has less propensity to cause visual disturbance on installation.

ACKNOWLEDGMENTS

We thank Dr Vincent Basgen and Dr Nakila Ibnou-Zehri for their advice. This study was sponsored by TRB Chemedica, Geneva, Switzerland. Michael Johnson was additionally supported by a research scholarship from Ultrasense Ltd.

Received June 10, 2007, accepted October 1, 2007.

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