SINGLEDOSOKANAMYCINTHERAPYOF
GONOCOCCALOPHTHALMIANEONATORUM

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Summary
117 infants with gonococcal ophthalmia neonatorum, including 27 with infections due to penicillinase-producing Neisseria gonorrhoeae, were treated as outpatients with five different regimens of single-dose intramuscular kanamycin (75 mg or 150 mg) with saline eye washes, gentamicin eye ointment, or chloramphenicol eye drops. There were no treatment failures among 68 patients treated with 75 mg or 150 mg kanamycin and gentamicin eye ointment (for 3 days). However, the minimum and maximum cumulative probabilities of cure of single-dose kanamycin with saline eye washes (for 3 days) were only 60% and 89%. 1 patient of 15 treated with 150 mg kanamycin plus chloramphenicol eye drops did not respond to treatment. Postgonococcal conjunctivitis developed in 14 (12%) infants, of whom 13 had positive cultures for Chlamydia trachomatis. Nasopharyngeal infection with N gonorrhoeae was eradicated in 9 of 11 infants colonised.

Introduction
Sexually transmitted diseases and their sequelae are very common in many areas of the developing world, where perinatal infections such as congenital syphilis and ophthalmia neonatorum are still important public health problems. Neisseria gonorrhoeae is the commonest cause of ophthalmia neonatorum in Africa, where eye prophylaxis is rarely used (and L. F. et al, unpublished). Gonococcal neonatal conjunctivitis is a serious disease, since it may cause blindness if untreated.

The recommended treatment regimens for gonococcal ophthalmia neonatorum include multiple doses of intravenous penicillin with or without topical antimicrobial therapy and hospital admission of the infant. Cefotaxime and gentamicin have been recommended in appropriate doses for the treatment of neonatal conjunctivitis due to penicillinase-producing N gonorrhoeae (PPNG). However, these regimens cannot be used in many developing countries, where PPNG infections are frequent, the numbers of hospital beds and of trained personnel are limited, and expensive drugs such as third-generation cephalosporins are not available. A cheap single-dose therapy which could be given at an outpatient clinic would be better adapted to the constraints of these health-care systems.

For these reasons, and because gonococcal ophthalmia neonatorum, including PPNG infections, is common in Kenya, we evaluated a single intramuscular dose of kanamycin for the treatment of this disease in an outpatient population. Kanamycin was selected since it is available in Kenya and since a single 500 mg intramuscular dose in combination with gentamicin eye ointment was reported to be effective for the treatment of gonococcal neonatal conjunctivitis in Singapore. Because of the controversy about the need to add topical antibiotics to systemic treatment for neonatal conjunctivitis, and because systemic therapy without topical antibiotics would be a major operational advantage, the effectiveness of intramuscular kanamycin with and without gentamicin eye ointment (kanamycin eye ointment was not available) was assessed in a randomised trial.

Patients and Methods
The eyes of all infants with neonatal conjunctivitis seen in 1983 at the Nairobi Special Treatment Clinic were examined by one clinician, and the severity of conjunctivitis was scored by Sandström's method on the more inflamed eye. An ophthalmia neonatorum case was defined as an infant younger than 30 days with abnormal ocular discharge from one or both eyes, and with at least one polymorphonuclear leucocyte per oil immersion field (1000×) on a gram-stained smear of the discharge.

Conjunctival swabs were cultured for N gonorrhoeae on modified Thayer-Martin agar, for Chlamydia trachomatis on cycloheximide-treated McCoy cells, for herpes simplex virus on fibroblast cells, and for facultative bacteria on blood agar. Additional specimens were obtained from the oropharynx and rectum for N gonorrhoeae and C trachomatis culture. All mothers and 74 fathers underwent genital and ocular examination, and cervical and urethral swabs were collected for N gonorrhoeae and C trachomatis culture.

Three treatment trials were conducted sequentially. In the first trial, 53 infants with gram-negativ diplococci on a conjunctival smear were assigned randomly to a single intramuscular dose of 75 mg kanamycin combined with topical gentamicin eye ointment (1%) half-hourly for the first 10 hours and then four times daily for 3 days (regimen A), or to a single 75 mg dose of kanamycin with saline eye washes applied in the same way and for the same time as the gentamicin ointment (regimen B). In a second study, 38 infants with gonococcal conjunctivitis were randomly assigned to a single intramuscular dose of 150 mg kanamycin in combination with gentamicin eye ointment for 3 days (regimen C) or saline eye washes for 3 days (regimen D). In the third study, 26 patients with gonococcal conjunctivitis were treated with a single intramuscular dose of 150 mg kanamycin in combination with either topical gentamicin ointment (regimen C) or chloramphenicol eye drops (regimen E), administered in the way described above. Topical treatment was administered by the mothers, who were instructed by a nurse.

Informed consent was obtained from each mother before treatment allocation. Mothers of babies with gonococcal conjunctivitis were treated at the initial visit with procaine eye drops.
and were retreated with spectinomycin 2 g in a single dose if the cultures showed penicillinase-producing strains. Fathers were treated according to microbiological results of urethral specimens.

The infants and their mothers returned for follow-up examination 3, 7, and 30 days after the initial visit. At each follow-up visit the baby’s eyes were assessed by the same criteria as at the initial visit, and the mother was given a gynaecological examination. All cultures were repeated in infants and mothers at least at days 3 and 30.

Minimum inhibitory concentrations of kanamycin, penicillin, gentamicin, chloramphenicol, and tetracycline were examined on 52 conjunctival N. gonorrhoeae isolates by an agar-dilution method on Mueller-Hinton agar base supplemented with 1% ‘IsoVitaleX’ (Baltimore Biological Laboratories, Cockeysville) and 5% lyced horse blood (Gibco Ltd, Paisley).

The cumulative probability of cure (CPC) was calculated after 3 and 30 days, as the number of cases cured divided by the number of cases treated. Since the treatment outcome is not known for patients lost to follow-up, two CPCs were calculated for each treatment group; CPC max assumes that all defaulters were cured and CPC min assumes that all defaulters represent treatment failures. The statistical significance of differences in CPC between treatment regimens was tested by Fisher’s exact test and by calculating the Student’s t test.

Results

The different treatment groups were comparable with regard to age, severity of conjunctivitis, duration of illness, birthweight, and the proportion of infections caused by PPNG strains (table 1).

The results of treatment with the different regimens are shown in table II. There were no bacteriological failures at day 3 or day 30 in the groups of infants who received 75 or 150 mg single-dose kanamycin in combination with gentamicin eye ointment (A and C). The CPC max (defaulters considered healed) and CPC min (defaulters considered treatment failures) of regimens A and C at 30 days were between 86-6% and 100%. In 8 patients in treatment groups (A and C) postgonococcal conjunctivitis had developed by day 3 after initiation of therapy with kanamycin-gentamicin. C. trachomatis was isolated in all cases at the initial visit and at the first follow-up visit.

Among the 15 infants treated with 75 mg kanamycin and saline eye washes (group B), 2 had persistent gonococcal conjunctivitis at day 3, and there were 2 bacteriological and clinical relapses at 10 days and at 30 days. In 1 of the babies with a persistent infection, pneumonia, sepsis, and a bilateral corneal ulcer developed. The CPC max and CPC min at 30 days for regimen B were 73% and 60%, respectively—significantly lower than those of regimen A (p<0.03 for CPC min). Among the 19 infants given kanamycin 150 mg and saline eye washes (group D), 1 had a persistent gonococcal conjunctivitis at day 3, and 1 relapsed clinically and bacteriologically at day 7. The CPC max and CPC min of this regimen were both 89-5% (not significantly different from those of regimen C). None of the N. gonorrhoeae strains isolated from treatment failures produced penicillinase.

In 2 group-D infants cured of conjunctivitis N. gonorrhoeae was isolated from the oropharynx, but not from the eye, 3 days after therapy. Chlamydial postgonococcal ophthalmia neonatorum developed in all 5 infants who had a positive C. trachomatis culture before treatment.

There was 1 persistent gonococcal infection at 3 days among the 15 patients treated with kanamycin 150 mg and chloramphenicol eye drops (group E), giving CPC max and CPC min at 30 days of 93% and 80%. Postgonococcal conjunctivitis developed in 1 infant at day 3.

The 7 patients who were not cured on any treatment regimen did not differ significantly from successfully treated cases in age, body weight, duration of symptoms, presence of cough or diarrhoea, and severity score at the initial visit. 2 of the 7 had N. gonorrhoeae isolated from the oropharynx, compared with 9 of 107 patients who responded successfully to treatment (not significant). Infants who were not cured with the kanamycin-saline regimen were cured when given kanamycin 150 mg combined with gentamicin, including the infants with N. gonorrhoeae isolated from the pharynx.

The in-vitro susceptibility of 52 gonococcal strains isolated from the eyes is shown in table III. Penicillinase production was detected in 23% of strains, while 9-3% of the penicillinase-negative isolates had a minimum inhibitory concentration of penicillin of 2 mg/l or more. All strains were moderately sensitive to kanamycin and gentamicin. Over half of the isolates had a minimum inhibitory concentration of tetracycline of 2-4 mg/l.

### Table I—Features of 117 Infants

<table>
<thead>
<tr>
<th>Feature</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>15</td>
<td>30</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Age (days)</td>
<td>12-3 ± 5.8</td>
<td>13 ± 5.7</td>
<td>9-1 ± 5.0</td>
<td>11-1 ± 5.0</td>
<td>9-1 ± 5.1</td>
</tr>
<tr>
<td>Duration of illness (days)</td>
<td>7-5 ± 2.7</td>
<td>7-4 ± 2.9</td>
<td>7-6 ± 0.6</td>
<td>5-9 ± 4.4</td>
<td>5-6 ± 2.5</td>
</tr>
<tr>
<td>Birthweight (kg)</td>
<td>3-4 ± 1.9</td>
<td>3-0 ± 2.4</td>
<td>2-9 ± 2.0</td>
<td>3-4 ± 0.9</td>
<td>2-9 ± 0.5</td>
</tr>
<tr>
<td>Conjunctivitis score</td>
<td>6-2 ± 1.4</td>
<td>6-2 ± 0.9</td>
<td>5-8 ± 1.5</td>
<td>5-8 ± 0.7</td>
<td>5-8 ± 1.1</td>
</tr>
<tr>
<td>No with N. gonorrhoeae isolated from pharynx</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>No (%) of PPNG strains</td>
<td>10 (28)</td>
<td>5 (20)</td>
<td>6 (20)</td>
<td>4 (21)</td>
<td>4 (27)</td>
</tr>
</tbody>
</table>

Infants from whom N. gonorrhoeae was reisolated or with a concomitant chlamydial infection are not included in the conjunctivitis score of the patients seen at the next follow-up visit.

CS = conjunctivitis score.

### Table II—Results of Treatment at Days 3 and 30

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 3</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No evaluated</td>
<td>N. gonorrhoeae isolated from eye</td>
</tr>
<tr>
<td>A</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>C</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>19</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table III—In-Vitro Susceptibility of 52 Neisseria gonorrhoeae Strains Isolated from Eyes of Infants with Ophthalmia Neonatorum

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Minimum inhibitory concentration (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>Range</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0-25-2</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>2-4</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0-015-4</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0-25-4</td>
</tr>
</tbody>
</table>

Minimum inhibitory concentration (mg/l)
Discussion

This study shows that a single dose of 75 or 150 mg kanamycin in association with 1% gentamicin eye ointment for 3 days is an effective treatment for ophthalmia neonatorum due to penicillin-sensitive and penicillinase-producing N. gonorrhoeae. This therapy can be given on an outpatient basis, with the mother administering the ointment. Single-dose kanamycin (500 mg intramuscularly) combined with kanamycin eye ointment cured all of 11 treated infants with gonococcal ophthalmia neonatorum in Singapore. However, such a high dose of kanamycin may be toxic for newborn infants, since serum levels above 50 μg/ml should be avoided (J. D. Nelson, personal communication). Although the ototoxicity of a single high serum level of kanamycin is not known, the risk of toxic effects on the ear is unlikely if the total dose does not exceed 500 mg/kg. Long-term evaluation of the potential ototoxicity of the doses of kanamycin we used is required.

Successful therapeutic results have been reported in 8 infants with gonococcal ophthalmia neonatorum due to beta-lactamase-producing strains. The treatment regimen used was a single parenteral dose of 75-150 mg kanamycin 1% eye ointment for 7 days; intramuscular cefotaxime 100 mg/kg daily and saline eye washes for 7 days; intravenous cephalixin for 2 days, then oral cephalixin and gentamicin eye drops for 3 days; single-dose intramuscular kanamycin 1 g and 1% kanamycin eyedrops; oral erythromycin syrup 40 mg/kg daily and chloramphenicol 1% eye ointment for 7 days; and intramuscular ceferoxime 100 mg/kg daily in three doses for 7 days.

For areas with a PPNG prevalence of more than 1%, the World Health Organisation recommends that ophthalmia neonatorum due to PPNG should be treated with cefotaxime 100 mg/kg as a single intramuscular dose or kanamycin 25 mg/kg as a single intramuscular dose with tetracycline 1% or erythromycin 0.5% eye ointment for 10 days. The Centers for Disease Control recommend hospital admission for at least 24 h and intravenous benzylpenicillin 50 000 U/kg daily in two doses for 7 days and saline eye irrigation. Cefotaxime and gentamicin in appropriate doses are recommended for neonatal PPNG infections.

However, these recommendations are not based on controlled clinical trials. The WHO regimen of single-dose kanamycin combined with topical tetracycline ointment most closely resembles the regimen we found effective. Its effectiveness remains to be proven, particularly in developing countries where a large proportion of gonococcal strains have minimum inhibitory concentrations of tetracycline of 2 mg/l and more. Since gentamicin eye ointment may be too expensive for many countries, the kanamycin-tetracycline regimen should be urgently evaluated. Our finding that postgonococcal conjunctivitis associated with C. trachomatis occurred in more than 10% of cases treated with drugs not effective against chlamydia may be further evidence for the addition of topical tetracycline therapy, since it may prevent postgonococcal conjunctivitis.

In our study, topical gentamicin eye ointment increased the cure rate of single-dose kanamycin, compared with the same dose of kanamycin given with saline eye washes only. The need for topical antibiotic treatment in ophthalmia neonatorum is controversial. Topical therapy with penicillin was originally thought to be adequate. However, antibiotic eye drops temporarily alleviate the signs of ophthalmia without eradicating the infection. In Singapore, nearly 20% of infants treated with penicillin eye drops only were not cured. Our finding that extraocular gonococcal infections occurred in 16% of these infants provides an additional argument for systemic treatment (unpublished).

A single parenteral dose of 75 mg kanamycin without topical antibiotics had an unacceptable failure rate in this study. Expected peak serum levels of kanamycin after a single intramuscular injection of 25 mg or 150 mg of the drug are 90-150 μg/ml in term infants for 4-7 h, and drug levels at the conjunctiva and cornea are unknown (McCracken and Nelson, personal communication). Thus, the 75-150 mg dose used may be under the minimum dose required to cure infections with N. gonorrhoeae strains with a minimum inhibitory concentration of kanamycin of 8-16 μg/ml, which may explain why systemic therapy combined with topical antibiotic treatment yielded a better cure rate. A single-dose treatment regimen without eye ointment or eye drops would be preferable, particularly in developing countries, since application of eye ointment or drops in a newborn is difficult, and compliance is uncertain. Higher doses of kanamycin, or single-dose therapy with highly effective antibiotic agents such as cefotaxime and ceftriaxone, both with saline eye washes only, may be effective for the treatment of gonococcal ophthalmia. The application of ophthalmic ointment in itself may increase the risk of conjunctivitis by introducing new organisms, as Mooney et al. observed.

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REFERENCES

4-HYDROXYANDROSTENDIONE IN TREATMENT OF POSTMENOPAUSAL PATIENTS WITH ADVANCED BREAST CANCER

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PAUL GOSS
MITCH DOWSETT
J-C. GAZET
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Summary 4-hydroxyandrostenedione, a potent inhibitor of the aromatase (oestrogen synthetase) system, was given to 11 patients with metastatic breast cancer. After a single 500 mg intramuscular injection a sustained reduction of serum oestradiol was observed for at least 1 week in all patients in whom the steroid was measured. 4 patients responded to treatment for periods of up to 4 months, and healing of bone metastases and reduction in size of soft-tissue metastases was evident. The only side-effects were pain at the injection site and hot flushes. 4-hydroxyandrostenedione is a new and specific aromatase inhibitor which shows promise in the treatment of patients with metastatic breast cancer.

Introduction

In postmenopausal and oophorectomised women oestrogen is mainly derived from the peripheral aromatisation of adrenal androgens in adipose tissue and muscle (fig 1). Inhibitors of the aromatase (oestrogen synthetase) enzyme system could therefore lower plasma oestrogens and may be more effective and safer alternatives than oophorectomy or adrenalectomy in patients with metastatic breast cancer.

4-hydroxyandrostenedione (4-OHA) (fig 2) is the most effective of several selective aromatase inhibitors and appears to be an active site-directed inhibitor. We have shown that 4-OHA inhibits ovarian aromatase oestrogen production and peripheral aromatisation in laboratory animals and causes regression of hormone-dependent carcinogen-induced tumours in the rat.

We report here the effect of 4-OHA in postmenopausal patients with advanced breast cancer.

Patients and Methods

Patients

Informed consent was obtained from all patients, and the study was approved by the Royal Marsden Hospital Ethics Committee; the Office for Protection from Research Risks, National Institute of Health, USA; and Human Volunteers Research Committee, University of Maryland School of Medicine, USA. 11 patients, age range 37–75, with histologically proven advanced progressive breast cancer were treated with 4-OHA for 3 to more than 20 weeks. 5 patients were postmenopausal and 6 had been oophorectomised (see table). None had received endocrine therapy or chemotherapy within 4 weeks of starting treatment. 5 patients are still being treated. 8 patients received weekly intramuscular injections of 4-OHA 500 mg, and 3 received fortnightly injections. Of 10 patients who had previously received endocrine therapy, 4 had responded but subsequently relapsed. Oestrogen-receptor analysis was carried out as previously described by means of the dextran-coated charcoal method for separating bound from free tritiated oestradiol, and results are available for 5 patients. Hormone-responsive tumours contain more than 15 fmol oestradiol per mg cytosol protein.

Patients were staged with standard methods before treatment and every 8 weeks during treatment. Response to treatment was measured according to the standard criteria of the International Union against Cancer.

Preparation of 4-OHA

4-OHA was synthesised as previously described and batches were purified by means of recrystallisation and combined. The melting point was 205–206°C and the extinction coefficient was 10,811: A max 278 nm. A portion of 4-OHA was analysed by means of thin-layer chromatography with ether:hexane (3:1) and then with benzene:ethyl acetate (85:15). Purification was repeated 3 times to separate the 4-OHA from the 4,5 epoxide. Only a single spot was visible with ultraviolet light, iodine vapour, and sulphuric-acid charring. Nuclear magnetic resonance and infra-red data were consistent with pure 4-OHA.

Fig 1—The sites of inhibition by 4-OHA in the conversion of cholesterol to oestradiol.