THE BRITISH JOURNAL OF OPHTHALMOLOGY

DECEMBER, 1948

COMMUNICATIONS

INTRAVITREAL INJECTION OF PENICILLIN: STUDY ON THE LEVELS OF CONCENTRATION REACHED AND THERAPEUTIC EFFICACY

BY

ARNOLD SORSBY *and* JOSEPH UNGAR

LONDON

DIRECT injection of penicillin into the vitreous was considered as a possible method of treatment in the early days of penicillin therapy, when it was held that penicillin injected systemically did not penetrate into the interior of the eye. The early samples of crude penicillin proved, however, highly destructive of the globe when injected intra-vitreally (von Sallmann, Meyer and di Grandi, 1944; Sorsby, 1945; Mann, 1946). In contrast crystalline penicillin is well tolerated (Sorsby and Ungar, 1946), though not altogether devoid of undesirable effects on the retina (Duguid *et al.*, 1947). As adequate therapeutic levels in the vitreous can now be obtained by subconjunctival injection (Sorsby and Ungar, 1946, 1947 and 1948), direct intravitreal injection of penicillin has become largely an academic question. In the following study an attempt is made

TABLE I
Levels (u/ml. or u/gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after intravitreal injection of 5,000 units of pure sodium penicillin into one eye.

	Injected Eye.									
	At	2 hours	4 hours	6 hours	18 hours	24 hours	36 hours	48 hours	64 hours	72 hours
Aqueous ...		> 8	160, >8	>8	> 8, 2, 8	> 8, 1	0.25	0, 0	0, 0	0, 0
Vitreous ...		> 8	>8, >8	>8	> 8, >32, > 32	> 8, 32	4	6, 1	0.06, tr.	0, 0
Anterior tissues		> 8	>15, >8	>8	>10, 80, >285	>12, 100	2.2	tr. tr.	0, 0	0, 0
Posterior tissues		>10	>12, >8	>8	>16, 80, >320	>11, 260	4	0, tr.	0, 0	0, 0
Blood ...		0	0, 0.06	0.06	0 — —	0 —	—	— —	— —	— —

NOTE—The different values recorded represent estimates in different animals.

to assess the levels and persistence of penicillin injected intravitreally and the efficacy of this procedure in controlling experimental vitreal infection.

1.—Level and persistence of penicillin on direct intravitreal injection

The pure sodium salt of penicillin was used, 5,000 units in 0.05 ml. being introduced by a tuberculin syringe directly into the vitreous, centrally at the equator of the right eye of fully grown rabbits. The animals were killed at 2, 4, 6, 18, 24, 36, 48, 64 and 72 hours, and the penicillin concentration in various ocular tissues determined by the standard capillary method of Fleming. The table (p. 858) shows the results obtained.

Three rabbits received injections of 5,000 units into the vitreous of both eyes. They were killed at 24, 48, and 64 hours respectively. The concentrations reached were not substantially different from those observed where one eye only had been injected.

TABLE II

Levels (u/ml or u/gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after intravitreal injection of 5,000 units of pure sodium penicillin into both eyes simultaneously.

	At	24 hours		48 hours		64 hours	
Aqueous		4,	1	tr.	tr.	0,	0
Vitreous		>32,	32	16,	4	0.06,	tr.
Anterior tissues		8,	20	0,	0	0,	0
Posterior tissues		140,	200	0,	1.5	0,	0

NOTE—Each set of two values represents the readings in the right and left eyes of a rabbit.

It would therefore appear that the direct intravitreal injection of 5,000 units pure penicillin gives an adequate intravitreal concentration up to 36 hours—or possibly up to 48 hours. Thereafter there is no penicillin left in the vitreous or other ocular tissues.

The uninjected left eye of those rabbits which received injections in the right only, occasionally showed small values suggestive of some diffusion locally or absorption systemically of the penicillin injected intravitreally.

TABLE III
Levels (μ /ml. or μ /gm.) of penicillin in the aqueous, vitreous, anterior tissues and posterior tissues of the globe at different times after the intravitreal injection of 5,000 units of pure sodium penicillin in one eye.

	Uninjected Eye									
	At	2 hours	4 hours	6 hours	18 hours	24 hours	36 hours	48 hours	64 hours	72 hours
Aqueous ...		8	0, 0'6	0'5, 0	0, 0'25, 0	0, 0	0, 0	0	0, 0	0, 0
Vitreous ...		8	0, 0	0, 0	0, 0'25, 0	0'06, 0'125	tr. 0	0	0, 0	0, 0
Anterior tissues		0'08	0, 0	0, 0	0, 0'4, 0	0, 0'3	0, 0	0	0, 0	0, 0
Posterior tissues		2	0, 0	0, 0	1'5, 0'4, 0	0, 0'3	0, 0	0	0, 0	0, 0
Blood ...		—	0, 0'06	0'06, 0	— — — 0	0 — —	— — —	— — —	— — —	— — —

NOTE—The different values recorded represent estimates in different animals.

2.—Control of experimental vitreous infection by intravitreal injection of penicillin

Material and technique.—Into the right eye of 12 rabbits each weighing 800-1,000 gms., 1,000,000 organisms of staphylococcus aureus strain 663 were injected in 0.05 ml. of saline. Three animals (Nos. 1-3) were kept as controls; 3 more (Nos. 4-6) had injections of 5,000 units of crystalline penicillin in 0.05 ml. of distilled water 20 hours after infection, whilst treatment was begun 3 hours, and immediately after infection in two further batches of 3 animals (Nos. 7-9 and 10-12 respectively). Both the infecting material and the penicillin were introduced centrally into the vitreous by a tuberculin syringe entered at the equator of the globe. Observations were continued over a period of 60 days.

Results

(1) Within the first 72 hours.

Controls (Nos. 1-3). Within 24 hours the vitreous assumed a yellowish reflex visible with the naked eye. The globes were greatly engorged. Twenty-four hours later the corneae were steamy and 24 hours later still panophthalmitis was fully established.

Rabbits treated 20 hours after infection (Nos. 4-6). Heavy vitreous involvement, seen with the naked eye, was present within 24 hours; the globes were grossly engorged. The subsequent course was only slightly less severe than in the control animals.

Rabbits treated 3 hours after infection (Nos. 7-9). No obvious vitreous reflex with the naked eye at 24 hours; some congestion of the globe was present. During the subsequent 2 days the inflammatory reaction became less obvious, though the eyes did not appear normal as congestion persisted.

Rabbits treated at the time of infection (Nos. 10-12). Twenty-four hours later the external appearance of the infected eyes was normal and remained so.

(2) On the fourth day after injection.

Controls (Nos. 1-3). All 3 animals showed heavy panophthalmitis. Number 2 was found dead, and the remaining two were destroyed.

Rabbits treated 20 hours after infection (Nos. 4-6). The globes were markedly injected. With the naked eye a greyish-yellow reflex was seen from the vitreous in rabbits Nos. 4 and 5, in No. 6 there was diffuse cloudiness of the cornea, precluding a view of the interior of the eye.

Rabbits treated 3 hours after infection (Nos. 7-9). Ophthalmoscopically the vitreous was organised in No. 8, and turbid with grey organised masses in rabbits Nos. 7 and 9. The globes were somewhat injected.

Rabbits treated at the time of infection (Nos. 10-12). The vitreous was turbid in all three rabbits on ophthalmoscopic examination. A red reflex was present in Nos. 11 and 12, though white opacities were also seen; in No. 10 the vitreous was as cloudy as in the rabbits treated 3 hours after infection.

(3) *On the 11th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4-6). One of these three (No. 5) had died 6 days previously. Of the two survivors, one (No. 6) showed a grossly infected eye with a steamy cornea. The second (No. 4) showed iritis with an organized vitreous.

Rabbits treated 3 hours after infection (Nos. 7-9). No. 7 showed a contracted pupil. There was a good red reflex, and some white vitreous opacities. No. 8 showed posterior synechiae and an organised vitreous. The condition of No. 9 was intermediate between that of No. 7 and No. 8; there was a red reflex, but fundus details were not visible.

Rabbits treated at the time of infection (Nos. 10-12). No. 12 had died 6 days previously. No. 10 showed a red reflex, but massive vitreous opacities, mainly white globules were also present. There were white exudates in the fundus below. The changes present were more severe than those seen in No. 9. In No. 11 there was a good red reflex, the pupil was fairly well dilated, but vitreous opacities and fundus reactions as in No. 10 were present.

(4) *On the 25th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4 and 6). Of the two surviving rabbits No. 4 showed a quiet eye with a partially occluded pupil and organized vitreous. No. 6 was very similar: the vitreous was a completely organised yellow mass.

Rabbits treated 3 hours after infection (Nos. 7-9). The result in No. 7 was excellent. The eye was quiet and the vitreous clear, except for two small residual opacities below. In the other two rabbits, the eyes were quiet; No. 8 showed a fairly massive opacity centrally in the vitreous, whilst in No. 9 there were diffuse vitreous opacities obstructing a view of the fundus.

Rabbits treated at the time of infection (Nos. 10 and 11). Both the surviving rabbits showed quiet eyes. In No. 10 the fundus could be seen readily, though there were still some vitreous

opacities. No. 11 was likewise satisfactory, but showed rather more vitreous opacity, and a localised fundus lesion below.

(5) *On the 46th day after infection.*

Rabbits treated 20 hours after infection (Nos. 4 and 6). In rabbit No. 4 the vitreous was completely organised. The animal was destroyed. In rabbit No. 6 the pupil was bound down, the vitreous organised and the cornea showed extensive infiltrates.

Rabbits treated 3 hours after infection (Nos. 7-9). Two of these rabbits (Nos. 7 and 9) showed little more than fine vitreous opacities. The eyes were regarded as good functioning organs clinically. Rabbit No. 8 on the other hand showed a fairly massive vitreous opacity.

Rabbits treated at the time of infection (Nos. 10 and 11). Rabbit No. 10 showed localised vitreous opacities with an extensive fundus lesion below. There was massive organisation of the vitreous in No. 11.

(6) *On the 60th day after infection.*

There were no substantial differences from the observations on the 46th day, except that Rabbit No. 11—one of those treated immediately after infection—now showed a grey reflex from organised vitreous, readily seen with the naked eye.

Comment

These results are not particularly encouraging. Only two of the three rabbits treated 3 hours after infection and only one, possibly two, of the three treated immediately after infection could be regarded as having good functioning eyes clinically. In the remaining animals the infected eyes were lost. It is clear that penicillin greatly influences the course of the infection, but it is also obvious that one intravitreal injection of 5,000 units is not sufficient to overcome fully a heavy experimental infection, though administered 3 hours after infection, or even at the time of infection. Treatment begun 20 hours after infection can prevent panophthalmitis at the expense of an organised vitreous which destroys the eye functionally. Repeated intravitreal injections begun early in mild infections might give better results, but the intolerance of the vitreous to any injections, and the apparent special liability to retinal damage from penicillin administered intravitreally, are serious limiting factors.

Summary

1. Adequate antibacterial levels persist in the vitreous for 36 hours and possibly 48 hours after direct intravitreal injection of 5,000 units crystalline penicillin in 0.05 ml. of water.

2. In heavy experimental infection of the vitreous (1,000,000 organisms of staphylococcus aureus)¹ 5,000 units crystalline penicillin injected into the vitreous had some slight effect if given 20 hours after infection; panophthalmitis was prevented but the vitreous was organised. When treatment was begun 3 hours, or immediately after infection, 3—possibly 4—out of 6 treated eyes could be regarded as clinically functioning eyes.

REFERENCES

- DUGUID, J. P., GINSBERG, M., FRASER, I. C., MACASKILL, J., MICHAELSON, I. C. and ROBSON, J. M. (1947).—*Brit. Jl. Ophthal.*, Vol. XXXI, 193.
 MANN, I. (1946).—*Brit. Jl. Ophthal.*, Vol. XXX, p. 134.
 SORSBY, A. (1945).—*Brit. Jl. Ophthal.*, Vol. XXIX, p. 511.
 SORSBY, A. and UNGAR, J. (1946).—*Brit. Med. Jl.*, ii, p. 723.
 ——— (1947).—*Brit. Jl. Ophthal.*, Vol. XXXI, p. 517.
 ——— (1948).—*Ibid.* This issue, p. 864.
 V. SALLMANN, L., MEYER, K. and DI GRANDI, J. (1944).—*Arch. Ophthal.* (Chicago), Vol. XXXII, p. 179.

DISTRIBUTION OF PENICILLIN IN THE EYE AFTER INJECTIONS OF 1,000,000 UNITS BY THE SUBCONJUNCTIVAL, RETROBULBAR AND INTRAMUSCULAR ROUTES

BY

ARNOLD SORSBY and JOSEPH UNGAR

LONDON

In earlier studies (Sorsby and Ungar, 1946 and 1947) it was shown that adequate therapeutic levels could be obtained intra-ocularly by injection of large doses of penicillin subconjunctivally. Attention was drawn to the fact that it was also possible to obtain adequate intra-ocular concentrations by systemic administration of massive doses. (Struble and Bellows, 1944; Town, Frisbe and Wisda, 1946; Town and Hunt, 1946; and Sorsby and Ungar, 1946.) It was also shown that the levels reached and maintained by subconjunctival injection were higher than those obtained by other routes. Subconjunctival injections gave higher and more persistent levels when the penicillin was dissolved in adrenalin solution 1:1,000 instead of water. There also emerged the fact that the use of 50,000 units as a subconjunctival dose tended to give not only higher but more persistent intra-ocular levels of concentration than with doses of 20,000 units.

The present study deals with the levels obtained when the dose of penicillin was 1,000,000 units injected subconjunctivally in