ANTI-INFLAMMATORY EFFECT OF OXYPHENBUTAZONE AFTER CATARACT AND SQUINT OPERATIONS*†

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ONE of the constant aims of the ophthalmic surgeon is to reduce post-operative inflammation to the minimum. The introduction of steroids has intensified interest in this problem. There is experimental evidence that steroids have a retarding effect on wound healing (Ashton and Cook, 1951; Newell and Dixon, 1951; Leopold, Purnell, Cannon, Steinmetz, and McDonald, 1951), but clinically this has not been confirmed (Woods, 1952; Dunnington, 1955), whereas their action in reducing inflammation in a non-specific fashion is more generally accepted (Gordon, McLean, and Koteen, 1953). Unfortunately, steroid therapy also has its complications and contraindications, notably steroid dependence on the continuation of therapy and the risk of infection by viruses and fungi or bacteria.

This has led to a search for substances with steroid-like actions that contained their virtues but not their vices. Oxyphenbutazone (Tanderil) may be regarded as one of these, combining pronounced anti-inflammatory activity with minimal disturbance of electrolyte or glucose metabolism and absence of dependence or the need for increased dosage.

In experimental animals, oxyphenbutazone has been shown to be effective in reducing sterile inflammations (Wilhelmi, 1960), and it has been suggested (Domenjoz, 1960) that part of its action is on the pituitary, thus causing adrenal stimulation. However, adrenalectomy does not seriously reduce the effectiveness of the drug, and it is probable that it also has a peripheral action, perhaps by reducing the increased capillary permeability found in inflammatory conditions. In addition, it has a central antipyretic and analgesic effect.

Oxyphenbutazone, a white powder insoluble in water, is soluble in alcohol and acetone; it is freely absorbed from the alimentary tract, although when taken by mouth it may prove to be a gastro-intestinal irritant and should be avoided when gastritis or peptic ulcer is suspected. Depression of the bone marrow may rarely occur, and the drug should not be given to patients with a history of blood dyscrasia or pyrazole sensitivity. Similar care should be taken with patients with cardiac, renal, or hepatic disease because of its mild but constant effect on electrolyte balance.

Clinically the drug has been used to reduce post-operative inflammation in dental and facio-maxillary surgery (Berghagen, Blom, and Kjellman, 1963), operations on the throat and nose (Catalano and Rossi, 1960), general surgery (Barcelo, Leblanc, Riopel, and Legresley, 1963), orthopaedic surgery (Allgöwer, Burri, Graffenried, Gruber, Heim, Meng, Segmüller, Siegrist, and Studer, 1963) and obstetrics and gynaecology (Fraser, Beardall, and Maughan, 1961).

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It has also been used by ophthalmologists for the treatment of medical conditions (Werner, 1960; Bannerjee and Taylor, 1961), and both Höpping (1963) and Gil del Rio (1962) used it to control post-operative inflammation after various surgical procedures. None of these reports, however, took the form of a double-blind trial and the present paper reports an attempt to meet this deficiency concerning the action of the drug as an anti-inflammatory agent following surgical trauma.

Material and Methods

Oxyphenbutazone was given to 63 patients, who were matched with 62 who received a placebo. In addition, all patients undergoing intra-ocular operations had routine post-operative medication, *i.e.* atropine and steroid drops and systemic antibiotics, and those who had extra-ocular operations received local penicillin drops. For all groups and ages (except those under 5 years of age) oxyphenbutazone 100 mg. or matching placebo tablets were used as follows:

Adults: two three times a day for 2 days followed by one four times a day.

Children 12–15 years inclusive: one four times a day for 2 days followed by one three times a day.

Children 8–11 years inclusive: one three times a day for 2 days followed by one twice a day.

Children 5–7 years inclusive: one twice a day for 2 days followed by one daily.

Children under 5 years: 50 mg. oxyphenbutazone suppositories one twice a day for 2 days followed by one daily. In this group the investigation was not double-blind and no placebo was used for the control group.

All treatment was started 24 hours pre-operatively, and the total period of treatment was 5 days only.

Approximately equal numbers of patients in each operation group received oxyphenbutazone or placebo tablets, this being predetermined by the method of allocation of the treatment.

To ensure that no patient with contraindications to the drug was admitted to the trial, a full history was taken and a general medical examination performed, together with urine examination, full blood count, and specific questions about contraindicatory conditions. Any patient with more than a minimal abnormality was excluded. Four patients were regarded as unsuitable and one patient aged 18 months was withdrawn from the trial because of anaesthetic difficulties. Of the four patients who were considered unsuitable, two had evidence of cardiac disease and two were due to have an operation on their only eye, and it was felt that the uncertainty of a clinical trial was not justified in these cases.

The operation site was assessed in terms of pain, swelling, and hyperaemia on the first, third, and sixth day after surgery. Examination on the first day indicated the degree of disturbance that the surgical trauma had caused; inspection on the third day attempted to measure the speed at which the normal post-operative inflammation was resolving, and that on the sixth day the incidence and severity of the later secondary complications.

It is recognized that inflammation may be described under the headings of rubor, dolor, calor, and tumor, but the eye does not lend itself to this classification very easily. It would, for example, be difficult to apportion the aqueous flare of iridocyclitis to any one of these headings. We have, therefore, classified our observations as degrees of pain, swelling, and hyperaemia. When we considered intra-ocular operations, conditions such as iritis, scleritis, or endophthalmitis fell under the heading of hyperaemia. For extra-ocular operations it applied to such conditions as orbital cellulitis, conjunctivitis, or cellulitis of the lid.

Assessment was purely clinical, carried out by both nursing and medical staff, and was

graded as severe, moderate, slight, or nil. Pain was assessed on the subjective evidence of the patient in addition to the objective impression of the examiners. In intra-ocular operations, hyperaemia was measured in terms of the clarity of the media, the degree of conjunctival and scleral injection, and the presence of inflammatory cells or exudates within the eye. In extra-ocular operations the conjunctival injection and colour of the skin and the presence of conjunctival exudates were the main factors considered. Swelling was assessed primarily in relation to the cornea, conjunctiva, and lids in intra-ocular procedures and of the conjunctiva, lids, and circumocular skin for extra-ocular procedures.

A total of 126 patients entered the trial, of whom 63 had oxyphenbutazone, 62 had placebo tablets, and one was withdrawn.

Operations.—46 patients had cataract extraction; 63 had correction of squint; eleven had other intra-ocular operations; five had extra-ocular operations. There were 55 males in the trial and 70 females. There were no significant differences between the oxyphenbutazone and placebo groups regarding operation, age, or sex distribution.

Results

If, regardless of operation, patients are first examined as two large groups, those who received oxyphenbutazone and those who received the placebo, the results for post-operative pain, swelling, and hyperaemia, are as follows:

Pain.—Only about 2 per cent. of the patients had any post-operative pain, and by the third day only four patients who received oxyphenbutazone and one who received the placebo were complaining of pain. There is no significant difference in these figures.

Swelling.—Table I shows the effect on post-operative swelling. At each examination day there were ten more patients with no post-operative swelling in the oxyphenbutazone group than in the control group. At all times fewer patients taking oxyphenbutazone had moderate or severe swelling, than in the control group. The differences (Figure, opposite) show a trend suggesting an anti-inflammatory action in the oxyphenbutazone group, but this is not statistically significant. (At the first and third day $0.10 > P > 0.05$ and at the sixth day $0.20 > P > 0.10$).

When patients under age 5 are excluded from Table I (for reasons which will be discussed later), these differences are more marked and are statistically significant on the sixth post-operative day ($0.05 > P > 0.02$).

TABLE I
POST-OPERATIVE SWELLING. ALL OPERATIONS

Day	Drug	Nil		Slight		Moderate		Severe		Total No.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
1	Oxyphenbutazone	35	55.6	15	23.8	13	20.6	0		63
	Placebo	25	40.3	20	32.3	15	24.2	2	3.2	62
3	Oxyphenbutazone	39	61.9	18	28.5	6	9.5	0		63
	Placebo	29	46.9	19	30.6	11	17.7	3	4.8	62
6	Oxyphenbutazone	49	77.8	10	15.9	4	6.3	0		63
	Placebo	39	62.9	6	25.8	6	9.7	1	1.6	62

FIGURE.—Effects of oxyphenbutazone on post-operative swelling compared with a placebo.

Hyperaemia.—Table II shows the effect on post-operative hyperaemia. The degree of hyperaemia was not affected by the drug in the immediate post-operative period, but by the third day the number of patients receiving oxyphenbutazone who had moderate or severe hyperaemia was smaller than that of those receiving the placebo, and this number had been greatly reduced (17 to 7) compared with the corresponding figures for the control group (15 to 18). These differences are statistically significant ($0.05 > P > 0.02$). On the sixth day, this trend was still evident.

TABLE II
POST-OPERATIVE HYPERAEMIA. ALL OPERATIONS

Day	Drug	Nil		Slight		Moderate		Severe		Total No.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
1	Oxyphenbutazone	6	9.5	40	63.5	17	26.8	0		63
	Placebo	6	9.7	41	66.1	15	24.2	0		62
3	Oxyphenbutazone	12	18.9	44	69.8	7	11.1	0		63
	Placebo	13	20.9	31	50	17	27.4	1	1.6	62
6	Oxyphenbutazone	26	41.3	32	50.8	4	6.3	1	1.5	63
	Placebo	17	27.4	34	54.8	10	16.1	1	1.6	62

These figures illustrate the more rapid resolution of hyperaemia in those receiving oxyphenbutazone and the tendency of marked hyperaemia to persist in those receiving the placebo.

The two major groups of operations may now be examined in more detail.

CATARACT EXTRACTION

46 patients had operations for cataract—23 in each treatment group. Nine who received oxyphenbutazone (39 per cent.) and seven who received the placebo (30 per

cent.) were males. The mean age was 65 ± 3.091 in the experimental group and 69 ± 2.43 in the control group. The age distribution in the two groups was similar.

Pain.—Post-operative pain was very slight and showed no significant differences between the two groups.

Post-operative Swelling (Table III).—The differences between the two groups is clear. 87 per cent. of the patients who received oxyphenbutazone had no swelling on the first day and third day compared with only 52 and 56 per cent. in the placebo group. These differences are statistically significant ($0.05 > P > 0.02$) and were still present on the sixth day.

On the first two examination days only three patients who received oxyphenbutazone had slight or moderate swelling, whereas at the same time nearly half of those who received the placebo came into this category.

TABLE III
POST-OPERATIVE SWELLING FOLLOWING CATARACT EXTRACTION

Day	Drug	Nil		Slight		Moderate		Severe		Total No.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
1	Oxyphenbutazone	20	86.9	2	8.7	1	4.4	0		23
	Placebo	12	52.1	4	17.4	7	30.4	0		23
3	Oxyphenbutazone	20	86.9	3	13.0	0		0		23
	Placebo	13	56.3	7	30.4	3	13.0	0		23
6	Oxyphenbutazone	21	91.3	2	8.7	0		0		23
	Placebo	16	69.6	6	26.1	0		1	4.3	23

Post-operative Hyperaemia.—The more rapid regression of hyperaemia between the third and sixth day in those patients receiving oxyphenbutazone is shown in Table IV; there is a marked difference in the numbers of patients without hyperaemia on the sixth day—eleven out of 23 (48 per cent.) who received oxyphenbutazone and six out of 23 (26 per cent.) who received the placebo; this difference is statistically significant ($0.05 > P > 0.02$). Also of interest in this analysis are the figures for those patients in whom post-operative hyperaemia was moderate or severe; on the third day there were six such patients who received the placebo, and on the sixth day there were five. No patients who were given oxyphenbutazone appeared in this category on either day.

TABLE IV
POST-OPERATIVE HYPERAEMIA FOLLOWING CATARACT EXTRACTION

Day	Drug	Nil		Slight		Moderate		Severe		Total No.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
1	Oxyphenbutazone	1	4.3	21	91.3	1	4.3	0		23
	Placebo	2	8.7	17	71.3	4	17.4	0		23
3	Oxyphenbutazone	5	21.7	18	78.3	0		0		23
	Placebo	6	26.1	11	47.8	5	21.7	1	4.3	23
6	Oxyphenbutazone	11	47.8	12	52.2	0		0		23
	Placebo	6	26.1	12	52.2	4	17.4	1	4.3	23

SQUINT OPERATIONS

In this category 33 patients received oxyphenbutazone and thirty the placebo. There was a preponderance of males in the former group (67 per cent.) and of females in the latter (60 per cent.). The mean age of the patients who received oxyphenbutazone was 8 ± 1.57 years and of the controls 12 ± 2.57 years. This difference is not statistically significant; the distribution of age groups was similar except there were five adults over 30 years of age who received the placebo and two who received oxyphenbutazone; this accounts for the difference in mean age between the groups.

Post-operative Swelling.—Initial examination of the data showed only small differences between the two groups; these mostly suggested an anti-inflammatory action in the oxyphenbutazone group. As the children under 5 years had been given an experimental form of the suppository, in rather low dosage, this group was examined separately, when almost identical figures were found for the oxyphenbutazone and placebo groups. Table V shows the incidence of post-operative swelling in these children under 5 years of age.

TABLE V
PERCENTAGE POST-OPERATIVE SWELLING AFTER SQUINT OPERATION IN CHILDREN UNDER 5 YEARS

Day	Drug	Nil	Slight	Moderate	Severe	Total
1	Oxyphenbutazone	50	35	14	0	99
	No oxyphenbutazone	46	39	15	0	100
3	Oxyphenbutazone	64	28	7	0	99
	No oxyphenbutazone	54	30	8	8	100
6	Oxyphenbutazone	72	21	7	0	100
	No oxyphenbutazone	84	8	8	0	100

The results when the children under 5 years of age are excluded are given in Table VI. By the sixth day after operation the swelling had subsided in a higher proportion of patients receiving oxyphenbutazone than in the control group, the difference being statistically significant ($0.05 > P > 0.02$). It is also marked when compared with the results in patients under 5 years of age. Similarly, there was a higher incidence of moderate or severe swelling on the third and sixth day in those who received the placebo than in those who received oxyphenbutazone, although this is not statistically significant.

TABLE VI
POST-OPERATIVE SWELLING IN SQUINT OPERATIONS IN PATIENTS OF 5 YEARS AND OVER

Day	Drug	Nil		Slight		Moderate		Severe		Total No.
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	
1	Oxyphenbutazone	5	26.3	7	36.8	7	36.8	0		19
	Placebo	5	29.4	6	35.2	5	29.4	1	5.9	17
3	Oxyphenbutazone	7	36.8	9	47.4	3	15.8	0		19
	Placebo	5	29.4	5	29.4	5	29.4	2	4.8	17
6	Oxyphenbutazone	14	73.7	2	10.5	3	15.8	0		19
	Placebo	6	35.2	7	41.4	4	23.5	0		17

Post-operative Hyperaemia.—Here the results were similar. Patients under 5 years of age gave almost identical results in the control and experimental groups. In those over 5 years old the results are not statistically significant, although those receiving oxyphenbutazone showed less hyperaemia on the sixth post-operative day.

OTHER OPERATIONS

In this group seven patients were treated with oxyphenbutazone and nine with the placebo.

Among the former the operations were: injection of an angioma (1), surgical correction of ptosis (1), dacryocystorhinostomy (1), discission (1), iridencleisis (3).

Among the latter they were: iridencleisis (3), discission (3), excision of pterygium (1), plastic repair to the eyelid (1), retinal detachment (1).

In view of the variation in operation and small numbers concerned, statistical analysis was not feasible.

SIDE-EFFECTS REPORTED DURING THE TRIAL

Only one patient complained of side-effects from the drug. This was a man aged 66 years who developed colicky abdominal pains and diarrhoea while receiving oxyphenbutazone. This rapidly subsided even while dosage of the drug was continued.

EFFECT ON WHITE CELL COUNT

It was intended that all patients should have a full blood count before and after treatment with oxyphenbutazone or the placebo. In fact, either the initial or the repeat count was omitted in 36 patients—seventeen in the oxyphenbutazone group, and nineteen in the placebo group. Analysis of the remaining counts showed no difference in number or degree of white cell counts which increased or decreased in the two groups.

Conclusions

In patients who underwent cataract extraction, post-operative swelling and to a lesser extent hyperaemia and injection were significantly reduced in the oxyphenbutazone group. Post-operative pain was absent in most cases and for this reason the analgesic effect of oxyphenbutazone, if any, could not be observed.

Patients having squint operations also benefited from oxyphenbutazone but not to such a marked degree. Swelling was more rapidly resolved, though hyperaemia was not so markedly affected. It is possible that the dosage in many of the children concerned may have been too small. For children the suppository form in this dosage was shown to be ineffective.

Summary

A double-blind trial comparing the anti-inflammatory effect of oxyphenbutazone (Tanderil) with a matching placebo on patients undergoing cataract and squint operations is described.

The results of the trial were subjected to statistical analysis.

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