

## HYDROXY-PHENYLBUTAZONE (TANDERIL) IN THE TREATMENT OF OCULAR DISEASE

### A PRELIMINARY SURVEY

BY

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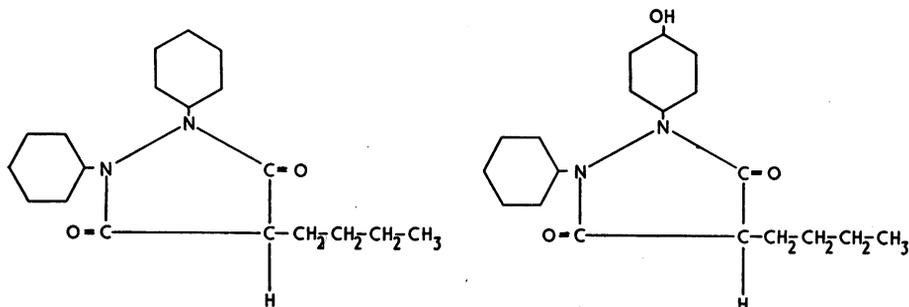
HYDROXY-PHENYLBUTAZONE (Tanderil) having proved in many cases an efficacious and less toxic substitute for phenylbutazone (Butazolidin) (Hart and Burley, 1959; Mason and Cramer, 1959), and having been noted by a rheumatologist (O'Reilly, 1958) to have a beneficial effect on iritis associated with rheumatic conditions, Messrs. Geigy have made a quantity available to me for the treatment of ocular diseases.

Svane-Knudsen (1959) described fifteen cases of ocular disease treated with phenylbutazone with rapid analgesic effect and acceleration of absorption of exudates. He remarked, however, on the necessity for caution in its use, owing to unpleasant side-effects including leucopenia and gastric ulceration.

Neither of these complications has been seen in any of my patients treated with the hydroxy derivative, even after a number of months, and temporary water retention in two cases has been only a minor inconvenience.

*Chemical Composition.*—Tanderil is a naturally-occurring metabolite of phenylbutazone. It was isolated in the urine of patients receiving the drug by Burns, Rose, Goodwin, Reichenthal, Horning, and Brodie (1955), and later synthesized in the laboratories of Messrs. J. R. Geigy in Basel (Pfister and Häfliger, 1957).

The compound has a hydroxyl group in the *para* position of benzene ring A of the phenylbutazone molecule. The structural formula of Tanderil and that of the parent substance phenylbutazone are given below:



Phenylbutazone (Butazolidin)      Hydroxy-phenylbutazone (G. 27 202) Tanderil

*Biochemistry.*—This has been studied by Burns and others (1955). Tanderil is fairly slowly but almost completely metabolized, the “half-life” being about 2 days—a little shorter than that of phenylbutazone.

*Pharmacology.*—This has been studied by Domenjoz and Wilhelmi (personal

communication). Toxicity studies have shown that Tanderil can be given to man within the usual limits of the pyrazoles.

It has been demonstrated in animal experiments that Tanderil has a more pronounced inhibitory effect on acute and chronic inflammation than the same dose of phenylbutazone; its antipyretic effect is stronger, and its analgesic effect similar. Animal studies have indicated that it also has much lower ulcerogenic effect.

### Material and Method

In an address delivered on the occasion of the award in 1958 of the Proctor Medal of the American Association for Research in Ophthalmology, Reese (1958) pointed out the manifold pitfalls into which the mere clinical investigator may fall, in putting forward what must of necessity be a summary of impressions rather than a controlled research project, but at the same time he gave a most heartening list of discoveries based on clinical observations alone.

One is at all times conscious of the difficulty of estimating the action of any new drug in a small number of conditions, in which the rate of improvement is so variable as in the majority of eyeball inflammations. With this point in mind, patients who (*a*) had been treated in previous attacks by other methods, or (*b*) had not responded during their present attack to other forms of treatment, were chosen for observation.

In an attempt to classify the results the following grades were defined:

Worse	Reacted less well than to previous treatment
Not Improved	No improvement with either treatment
Same	Recovery rate approximately the same
Better	Progress much better with Tanderil
Rapid	Rapid improvement, greatly in excess of that anticipated

### Results

#### (A) CHRONIC IRIDOCYCLITIS

The largest batch of patients investigated comprised thirteen cases of chronic iridocyclitis, probably the most disheartening of all ocular conditions to treat. The results were:

Worse	Nil
Not Improved	3
Same	2
Better	4
Rapid	4

All were cases in which no systemic or focal cause had been found for the condition. All had been treated primarily with topical corticosteroids and systemic Achromycin and Sulphatriad, followed by prednisone 5 mg. three times a day orally for at least 2 months. After this the topical treatment was continued, but 100 mg. Tanderil were given orally three times a day in place of the corticosteroids.

*Nor Improved (3).*—These were all cases of old choroiditis accompanying the iridocyclitis. There were dense vitreous opacities and the vitreous showed extensive disorganization on slit-lamp examination. Neither form of treatment had any effect.

*Same (23).*—These had been maintained inactive, or at a low level of activity, with varying amounts of oral corticosteroid for 4 to 6 months. A change to Tanderil controlled the condition no better and no worse.

*Better (4).*—These showed considerable activity. The visual acuity, the amount of keratic precipitates, and the vitreous opacities had remained unchanged for 8 weeks. After 4 weeks Tanderil therapy, the keratic precipitates were much less, and the visual acuity in three eyes improved as follows: 6/24 to 6/9, 3/60 to 6/24, 6/60 to 6/18.

*Rapid (4).*—Here the condition was chronic with acute exacerbations, the latter being very difficult to control.

The treatment hitherto employed had included salicylates, protein shock, oral prednisone, and local treatment.

The attacks were associated with severe pain and a rise in ocular tension, the latter usually requiring the use of Diamox which was not always successful. With Tanderil, pain was relieved in 24 hours, tension was of little consequence, and the whole acute phase was over in 3 days.

One of these patients had spondylitis, and might therefore be expected to be of a type particularly sensitive to phenylbutazone or allied compounds.

## (B) ACUTE IRITIS

Four cases were treated: one was worse, one was the same, and two rapid.

*Worse (1).*—This was the only one in the whole series of cases in which Tanderil was less satisfactory than the previous forms of treatment.

A man aged 52 had recurrent attacks of iritis with exudation into the anterior chamber and accompanying non-gonococcal urethritis, probably Reiter's disease. Previous attacks had responded in 1 week to local treatment plus sulphamezathine. There was little improvement after 10 days on Tanderil and when sulphamezathine was used at the patient's request the usual rapid resolution occurred.

*Same (1).*—A woman aged 48 had recurrent attacks of moderate severity. Tanderil plus local treatment had the same effect as Sulphatriad or prednisone.

### *Rapid (2)*

(i) Acute iridocyclitis occurred in an elderly female diabetic, with gross exudate in the anterior chamber (2 mm. deposit) and raised ocular tension. Local treatment was given plus sulphamezathine and there was no change in 5 days. A response to Tanderil occurred in 24 hours. The anterior chamber became clear in 48 hrs and the ocular tension became normal. This patient exhibited marked water retention, sometimes a minor disadvantage of the drug. Her ankles became swollen in 3 days, and after 6 days she was unable to fasten clothes around her waist. She informed me at this stage that she had had one kidney removed, and had stones in the other, so that in her case water retention was not surprising. Her eye was so well that Tanderil was stopped immediately, and within 3 days the water retention had gone without having to introduce diuretics.

(ii) A woman aged 40 with acute iritis had a history of previous attacks which had always responded in 10 to 14 days to mydriatics and local cortisone, but the present attack was unrelieved after 3 weeks of such treatment. After Tanderil the pain had gone in 48 hrs; the eye was much quieter, and became white in 4 days.

A small number of cases of acute iritis was treated because assessment of the value of treatment is particularly difficult.

Dr. O'Reilly, who has treated a number of cases of rheumatism with Tanderil, tells me that, in those who had an associated iritis unresponsive to other systemic treatment, the change to Tanderil nearly always produced a remarkable improvement.

### (C) KERATITIS

Four cases were treated and all showed rapid improvement.

(i) Deep keratitis and secondary iritis with visual acuity 4/60. Tanderil three times daily brought relief of pain in 48 hours, and lessening of corneal infiltration. After 3 weeks the visual acuity was 6/24 and in 6 weeks it was 6/9.

(ii) Deep sclero-keratitis. When first seen this patient had been under treatment with local and systemic cortisone and mydriatics for 3 weeks. Tanderil gave relief of severe pain in 12 hours, and in 48 hours the injection was less and the infiltration much less.

(iii) Deep keratitis associated with pulmonary tuberculosis. This had been controlled with difficulty by Streptopas injections and local cortisone. Recurrences previously lasted 2 to 3 months, but a severe flare-up settled down in 2 weeks with Tanderil and there has been no relapse for 3 months.

(iv) Patch of deep keratitis with painful secondary iritis and a history of recurrent attacks associated with spondylitis, demonstrated by x-ray findings in the spine. The attacks had been controlled in the past by local cortisone and mydriatics, but the latest attack had lasted 3 weeks with no sign of clearing. Tanderil gave almost immediate relief of pain. The eye was white and the infiltration almost gone in 3 days.

Ankle swelling occurred for the first 2 days, but disappeared when the dose was reduced from 300 to 200 mg. daily.

### (D) EPISCLERITIS

Two mild cases were treated and responded in 7 and 10 days respectively, but no more rapidly than would have been expected with other treatment such as topical corticosteroids and salicylates.

### (E) NODULAR SCLERITIS

Two cases were treated and both cleared rapidly.

(i) A girl aged 18, with raised nodules in both eyes opposite the rectus muscle insertions, had been under treatment with topical corticosteroids and Multivite orally for 4 to 5 weeks without change. Tanderil brought about rapid flattening of the nodules within 2 weeks, and an almost total return to normal of the sclera in 5 weeks. During treatment a small new spot appeared in one eye but disappeared in a few days.

(ii) A large raised nodular area almost surrounded the limbus in one eye. There was a history of previous similar attacks lasting 2 to 3 months on treatment with local corticosteroids. Treatment with Tanderil and local prednisone made the patient much more comfortable, and surprised at the rapidity of progress in 48 hrs. The raised areas were noticeably less in 3 days, and almost flat after 2 weeks, but the sclera was still discoloured.

### (F) SARCOID

Two cases were treated, but it was difficult to assess the result.

(i) Bilateral iridocyclitis with nodules on the iris in the left eye. A chest x-ray was positive, the Mantoux reaction negative, and the erythrocyte sedimentation rate 38 mm./hr

(Westergren). The visual acuity in the right eye was 6/60 and in the left 6/24. Mydriatics, topical prednisone, and Tanderil were given.

After 2 weeks the iris nodules had almost gone, the keratic precipitates were clearing, and the vitreous was clearer; the visual acuity in the left eye had improved to 6/9.

The patient was discharged from hospital with topical and systemic prednisone, as supplies of Tanderil were short. After 5 weeks at home, the patient became ill with acute abdominal pain and the systemic treatment was discontinued. On re-admission after 2 months there were fresh keratic precipitates and new nodules on the iris, and the visual acuity had deteriorated to 6/36. Treatment with local prednisone and Tanderil was recommenced, and in 3 weeks the iris nodules had gone, and the visual acuity was 6/9. The patient was then sent home again with prednisone drops and Tanderil 100 mg. three times daily.

(ii) Bilateral cyclitis with deep keratitis in one eye. A chest x-ray was positive, the Mantoux reaction negative, and the erythrocyte sedimentation rate was 28 mm./hr (Westergren). There was no change after 2 weeks treatment with topical prednisone; Tanderil was then started and after 2 weeks the keratitis was inactive, the eyes white, and the keratic precipitates lessening. The patient was discharged with local prednisone and Tanderil, and after 2 months both eyes were free from inflammation, with little corneal scarring and only slight pigmentary remains of the keratic precipitates.

#### (G) PERIPHLEBITIS RETINAE

Three long-established cases showed no improvement. Although no fresh bleeding occurred during the 2 months that they were under treatment, there was neither improvement in vision nor apparent reduction in vitreous opacities.

#### (H) HERPES ZOSTER OPHTHALMICUS

One long-standing case was treated for 3 weeks for post-herpetic neuralgia with no apparent benefit, although from one's short experience of other conditions it would seem likely that Tanderil in the early stages might diminish pain and damp down ocular reactions.

#### (I) POST-INFLUENZAL RETROBULBAR PAIN

Three cases showed no improvement after an influenza epidemic in which retrobulbar pain was a feature during convalescence. Tanderil seemed to be no more efficacious than aspirin.

#### SUMMARY

34 cases of ocular disease were treated over a period of 6 months with hydroxy-phenylbutazone (Tanderil). The action of this drug in suppressing inflammation seems to be similar to that of the salicylates and corticosteroids, with certain probable advantages.

With what appears to be an adequate dosage (300 mg. daily) there was almost complete absence of toxic side-effects, and the drug could be continued safely for as long as 12 months (as shown by Hart, 1959).

Its analgesic effect in some cases is a benefit not usually conferred by corticosteroids, and there are no withdrawal phenomena.

In the cases of deep keratitis and nodular scleritis in which it was tried, its resolvent and analgesic effects were remarkable.

In two cases of sarcoidosis its effect seemed identical with, or slightly superior to, that of corticosteroids.

In cases with active inflammatory exudates in the vitreous the rate of absorption seemed more rapid than one would normally expect, but in post-haemorrhagic cases, or where exudation was already organized, no improvement took place.

My thanks are due to Dr. W. S. Stoddart of the Clinical Research Department, Geigy Pharmaceuticals Ltd. both for his help in the preparation of this survey, and for the very generous quantities of the drug supplied for investigation.

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#### ADDENDUM

Since the paper was written, 23 further cases of uveitis, scleritis, and deep keratitis have been treated with Tanderil over periods varying from 1 month to 4 months, without appreciable side-effects, and with disappearance of inflammatory manifestations in all of them.

In three cases of herpes ophthalmicus no effect in controlling herpetic pain was found, but in two of these with raised scleral nodules and keratitis, marked improvement was manifest in 3 to 4 days with the usual dose of 100 mg. three times a day. When treatment was stopped after 2 weeks, recrudescence of the condition occurred and treatment had to be recommenced. There was, once again, rapid improvement, and both patients were kept on 300 mg., daily for a further 6 weeks, after which no further relapse took place.

This tendency to relapse on cessation of treatment, similar to one's experience with the systemic administration of cortisone was noted in eight cases in the new series.

In view of the fact that patients with ankylosing spondylitis provided a large proportion of the cases with positive findings reported by Perkins (1958) from the Uveitis Clinic at the Institute of Ophthalmology, it is interesting to study the paper of Graham (1960), who reported 353 patients with varying rheumatic conditions treated with Tanderil. Graham found that in ankylosing spondylitis there was a 90 per cent. response to treatment, and that in 250 complete blood studies carried out at intervals during treatment there was no evidence of any toxic effects on blood or marrow.

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