From: The Department of Dental and Oral Surgery. (Head: Professor E. Husted, M. D.), The Royal Dental College, Copenhagen, Denmark.

THE EFFECT OF G. 27202 (TANDERIL®, GEIGY) ON POST-OPERATIVE DISCOMFORT FOLLOWING REMOVAL OF THE LOWER THIRD MOLAR

by

E. Husted

E. Hjørting-Hansen

G. 27202 is hydroxy-phenylbutazone which is a metabolite of phenylbutazone (Butazolidin) and was first demonstrated in the urine of patients treated with phenylbutazone by *Burns* and his co-workers in 1955. The preparation is manufactured synthetically by the firm J. R. Geigy in Basel. The substance is of interest because it appears to have retained a considerable proportion of the valuable qualities of phenylbutazone and only relatively few of the less fortunate side-effects which limit the possibilities of employment of phenylbutazone in clinical practice. These side-effects consist primarily of blood changes (agranulocytosis and thrombocytopenia), nervous symptoms of central origin and symptoms from the gastro-intestinal tract (gastric and duodenal ulceration, possible perforation of pre-existing ulcer) and, further, retention of Na and water possibly with resulting oedema (as with cortisone) and exanthemata.

By means of chemico-pharmacological investigations and animal experiments (*Burns, Paton et al., Wilhelmi, Domenjoz*) and by clinical investigation, it was demonstrated that G. 27202 is resorbed rapidly and completely following oral administration. The half-lifetime is 48—72 hours and the total excretion takes approximately eight days. Dosage of 800 mg daily produces a maximal concentration in the blood of 8—15 mg %.

After animal experiments had revealed definite anti-inflammatory and antipyretic effects, clinical investigations have been undertaken mainly in patients suffering from rheumatic complaints. *Connel & Rousselot* treated 55 patients for a few days with 300—400 mg daily with good effect and without toxic symptoms. In a more limited material, the treatment was tried after various moderately severe operative interventions with the result that "post-operative pain was reduced to slight discomfort". Similar investigations were carried out by *Jarløv, Neil Cardoe, Vaughan, Howell & Kiem, Dudley Hart & Denis Burley, Barczyk & Röth* among others. The doses of G. 27202 were most frequently 300—400 mg daily for weeks. Prolonged therapy (300—400 mg daily for 4 to 18 months) was employed by *Jarløv* and by *O'Reilly* without the development of serious toxic symptoms necessitating withdrawal of the treatment.

Gigglberger treated 60 patients for 1—2 weeks with 300—500 mg daily particularly with a view to possible liver damage. No clinical side-effects were observed and, in particular, no blood changes or alterations in liver function. The results of the treatment are described as "good".

In maxillo-facial and similar branches of surgery, very little experience is, as yet, available. *Pfeifer* tried the effect of hydroxyphenylbutazone in doses of 600 mg daily for three days in 97 patients who had been submitted to operations on the jaws, mainly Caldwell-Luc's operation, and the effects on the post-operative pain and oedema were good. *Cancura* administered doses of 300—500 mg for three days to 130 patients in connection with tonsillectomy while a further 130 patients were operated upon in the same manner as controls but without administration of hydroxy-phenylbutazone. Considerably lesser quantities of analgesic drugs were required in the treated patients than in the control group. No side-effects were observed.

Werner treated 34 patients afflicted with various eye conditions with doses of 300 mg daily for "a number of months" with good effect and "almost complete absence of toxic side-effects".

According to all the evidence, although the experimental series are as yet rather limited, it appears probable that hydroxyphenylbutazone (Tanderil®) is a substance with antiphlogistic and antipyretic effects similar to those of phenylbutazone (Buta-

zolidin), but with considerably fewer side-effects. It seems desirable that the drug be submitted to more extensive clinical trial. When administration is prolonged (i.e. for more than a few days) the possibility of toxic effects upon the blood (agranulocytosis, thrombocytopenia) should be borne in mind and the drug must be considered to be contraindicated in patients with symptoms of peptic ulceration.

The pronounced analgesic effect of hydroxy-phenylbutazone must be due to its anti-inflammatory effect as the drug has no central analgesic effect.

In the Department of Dental and Oral Surgery, The Royal Dental College, Copenhagen, G. 27202 has been submitted to clinical trial for approximately one year following operative removal of lower third molars. This operation is so common that it is possible to collect a large experimental and control material within a reasonable period of time, and considerable experience is also available regarding the usual post-operative course. The material comprises 100 patients treated with G. 27202 and 100 control patients. The patients in the test material received a total of 13×100 mg of the drug distributed over four days: 3×100 mg on the day prior to operation, 4×100 mg on the day of operation and 3×100 mg on the two subsequent days.*) The control patients received a placebo, the tablets being of the same number, size, shape and colour but consisting of an inert substance (lactose). The experiment was carried out as a double-blind trial so that neither the patients nor the dentists treating or observing them were aware whether the patient concerned had received G. 27202 or the placebo.

During the post-operative period, the patients received the analgesic routinely employed in this department (Codeiphen DAK®) in tablet form. Control examination was undertaken one, three and five or six days after operation. For assessment of the effect, the following criteria were employed: pain, oedema and reduction of the ability to open the mouth. Further, careful in-

*) G. 27202 (Tanderil®) for these experiments was kindly supplied by J. R. Geigy A. G., Basel, Switzerland.

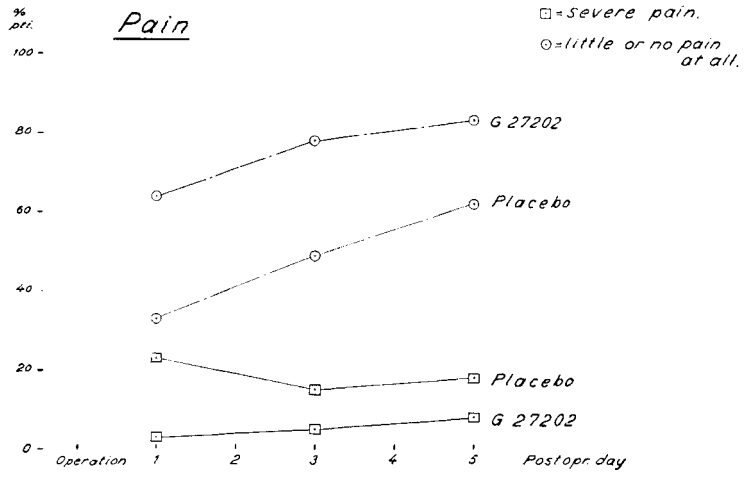

Fig. 1.

quiries were made regarding toxic side-effects. Blood examinations were not undertaken as it was considered that a dosage such as that employed here could not be expected to have any significance in this respect.

Pain was assessed according to the description given by the patients and the number of analgesic tablets required. The results will be seen from Figs. 1 and 2. Fig. 1 shows both the (limited) patient group who experienced severe pain and the (larger) group who experienced minimal pain or who did not complain of pain at all. Fig. 1 does not include all of the patients as the intermediate group of patients with moderate pain are not considered. It appears definitely from Fig. 1 that in the G. 27202 group there were approximately twice as many patients with minimal pain as in the control group and that very few of the treated patients had severe pain as compared with about twice as many in the control group.

Parallel to this, Fig. 2 shows a considerably lower employment of analgesics in the treated group as compared with the control group. On an average, the treated patients employed 2.6 tablets on the first day, 1.9 tablets on the third day and 1.9 tablets on

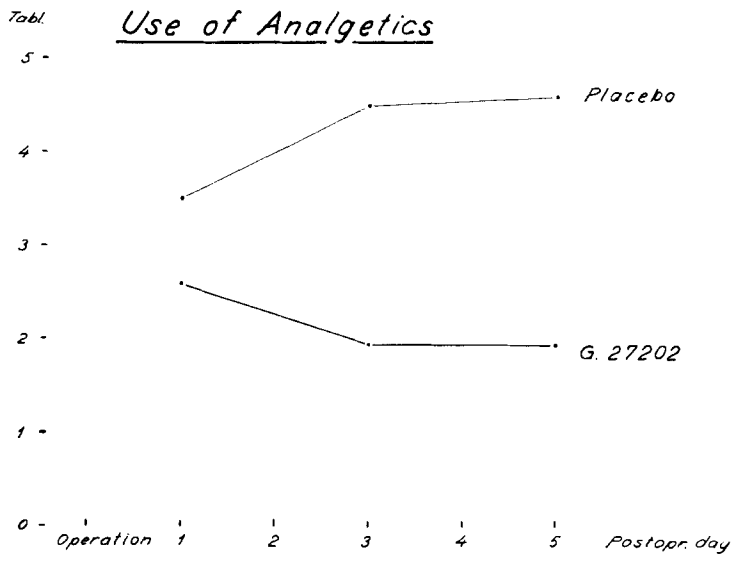

Fig. 2.

the fifth day while the control patients used 3.5, 4.5 and 4.6 tablets, respectively.

Constrictio maxillarum. The extent of opening of the mouth is expressed by the distance in mm between the incisal edges of the incisors when the mouth was opened as widely as possible. In Fig. 3 both a patient group in whom the ability to open the mouth was greatly reduced (by more than 20 mm as compared with the condition prior to operation) and a patient group with slight reduction (0—10 mm) are recorded. The intermediate group with reduction of 10—20 mm is thus not recorded in Fig. 2. It will be observed that there is no definite difference between the treated patients and the control patients. During the first 24 hours, however, there appears to be a greater tendency to constriction in the treated group but this difference is evened out between the third and fifth days.

Oedema was assessed purely clinically according to the size and extent of the swelling. Here also, conditions were the same

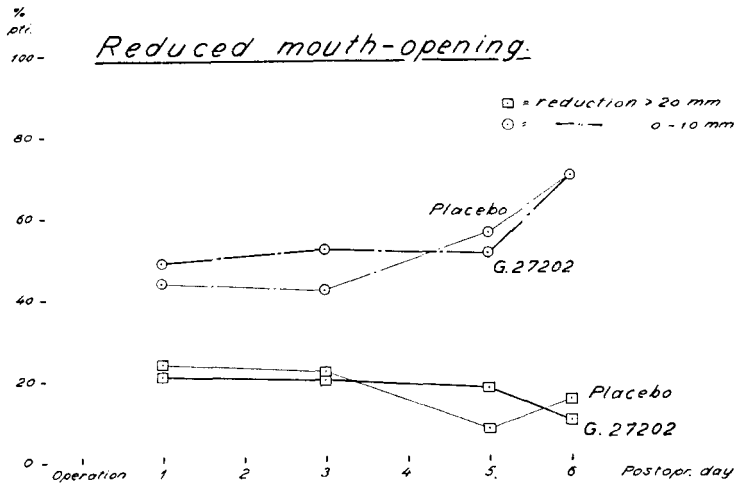

Fig. 3.

as for constriction, viz. there was no definite difference between the two groups.

Healing of the wound proceeded without any demonstrable difference in the two groups. In both groups, the wounds healed by first intention in approximately half of the cases while in the remainder of the cases gauze or another form of drainage had been introduced into the wound for a brief period or, in exceptional cases, for a more prolonged period either from the beginning or later on due to existing infection or infection developing later. Neither local nor systemic chemotherapy was employed in any case in connection with the operation. Severe pain associated with protracted healing of the wound occurred more frequently in the control group than in the treated group (proportion 3: 2).

In a total of three patients, marked post-operative haemorrhage occurred on the day after operation. Two patients from the control group and one of the treated patients were concerned.

Four of the treated patients had slight allergic reactions (exanthemata and slight diarrhoea) but not to such an extent that treatment had to be withdrawn or that the post-operative course was influenced. Two out of these four patients were known to be

allergic and should not, therefore, have been included in the experiment. Similar slight complications occurred in two patients in the control group.

CONCLUSION

G. 27202 (Tanderil®) has a considerable effect in reducing the post-operative pain following removal of impacted lower third molars. In the dosage employed in the present trial, no undesirable side-effects of significance were observed. The preparation would probably also be suitable following other operative interventions on the jaws which experience has shown to be associated with not inconsiderable post-operative pain.

SUMMARY

Tanderil® (hydroxy-phenyl butazone) was submitted to clinical trial in 100 patients in whom operative removal of impacted lower third molars was undertaken. As a control material, 100 patients were studied. These patients were operated upon in the same manner but Tanderil® was replaced by a placebo. The experiment was conducted as a double blind trial: neither the patients nor the dentists treating or observing them were aware whether Tanderil® or the placebo were employed.

The course was evaluated in respect of oedema, reduced ability to open the mouth and post-operative pain as judged by the employment of analgesics by the patients.

In all respects, but particularly as regards pain, Tanderil® appears to influence the post-operative course favourably. No undesirable side-effects were observed.

RÉSUMÉ

ACTION DE G. 27202 (TANDÉRIL®, GEIGY) SUR LES PHÉNOMÈNES POST-OPÉRATOIRES CONSÉCUTIFS À L'ABLATION CHIRURGICALE DE LA DENT DE SAGESSE INFÉRIEURE

Le Tandéril® (hydroxy-phényl butazone) a été soumis à des essais cliniques chez 100 patients à l'occasion de l'ablation chirurgicale d'une dent de sagesse incluse au maxillaire inférieur.

Le contrôle a été effectué sur 100 autres patients. Ces patients ont été opérés de la même manière, mais le Tandéril® a été remplacé par un placebo. L'expérience a été menée sous forme d'un double contrôle dans lequel ni les patients ni les dentistes faisant les traitements et les observations cliniques ne savaient si on avait employé le Tandéril® ou un placebo.

L'évolution a été jugée en ce qui concerne l'œdème, la constriction des mâchoires et la douleur post-opératoire telle qu'il était possible de l'évaluer d'après la quantité d'analgésiques absorbés par les patients.

A tous points de vue, mais particulièrement en ce qui concerne la douleur, le Tandéril® s'est révélé capable d'influencer favorablement l'évolution post-operatoire. Aucun effet secondaire indésirable n'a été observé.

ZUSAMMENFASSUNG

ÜBER DEN EINFLUSS VON G. 27202 (TANDERIL®, GEIGY) AUF DIE POSTOPERATIVEN BESCHWERDEN NACH CHIRURGISCHER ENTFERNUNG VON UNTEREN WEISHEITSZÄHNEN

Es wurde eine klinische Untersuchung über Tanderil® (hydroxy-phenyl butazone) durchgeführt. Das Material bestand aus 100 Patienten, bei denen man einen retinierten Weisheitszahn im Unterkiefer entfernt hatte. Als Kontrollmaterial wurden andere 100 Patienten herangezogen. Diese Patienten waren in derselben Weise operiert worden, aber bei ihnen wurde Tanderil® durch ein Placebo ersetzt. Die Untersuchung wurde als ein doppelter Blindtest durchgeführt, so dass weder Patienten noch Zahnärzte wussten, ob Tanderil® oder Placebo benutzt wurde.

Der postoperative Verlauf wurde mit Bezug auf Schwellung, eingeschränkte Mundöffnung und Schmerzen beurteilt. Bei der Beurteilung der Schmerzen ist man von dem Gebrauch von Analgetica ausgegangen.

In jeder Beziehung, besonders aber was die Schmerzen betrifft, scheint Tanderil® den postoperativen Verlauf günstig zu beeinflussen. Es wurden keine unerwünschten Nebenwirkungen beobachtet.

REFERENCES

Barczyk, W & G. Röth, 1960:Klinische Erfahrungen mit dem Antiphlogistikum G. 27202. Schweiz. Rundsch. Med. *49:* 589—91.

Burns, J. J., Rose K. Rose et al., 1955: The metabolic fate of phenylbutazone (Butazolidin) in man. J. Pharmacol. exp. Ther. *113:* 481—89.

Cancura, W., 1960: Über die klinische Erprobung des neuen Antiphlogisticums G. 27202 im Rahmen der Tonsillektomie. Ther. Umsch. *17:* 314—15.

Cardoe, N., 1959: Controlled trial of G. 27202 (p-hydroxyphenylbutazone) in rheumatoid arthritis. Ann. rheum.. Dis. *18:* 244—48.

Connell, James F & Louis M. Rousselot, 1959: The clinical evaluation of a new anti-inflammatory agent. Amer. J. Surg. *98:* 31—33.

Domenjoz, R., 1960: The pharmacology of phenylbutazone analogues. Ann. N. Y. Acad. of Sci. *86:* 263—91.

Gigglberger, H., 1960: Vorläufiger Bericht über die Prüfung der Leberverträglichkeit einer neuen entzündungshemmenden Substanz (G 27202). Praxis. *49:* 1233.

Hart, F. Dudley & Denis Burley, 1959: Phenylbutazone and its derivatives. With special reference to G. 27202. Brit. med. J. *I:* 1087—89.

Jarløv, N. V., 1960: Tanderil (G 27202) in the treatment of the rheumatic diseases. Acta rheum. scand. *6:* 174—78.

O'Reilly, T. J., 1960: Long-term treatment with the anti-rheumatic drug G 27202. J. Irish med. Ass. *46:* 106—107.

Ffeifer, H., 1960: Über den Einfluss entzündungshemmender Substanzen nach Kieferoperationen. Schweiz. Mschr. Zahnheilk. *70:* 899—903.

Vaughan, Phyllis P., David S. Howell & Iris M. Kiem, 1959: The comparative effects of phenylbutazone and G 27202 (Metabolite I) in patients with rheumatoid arthritis: An Assessment of methods for antirheumatic drug evaluation. Athr. and Rheum. *2:* 212—23.

Werner, L. E. J., 1960: Hydroxy-phenylbutazone (Tanderil) in the treatment of ocular disease. Brit. J. Ophthal. *44:* 755—60.

Wilhelmi, G., 1960: Die pharmakologischen Eigenschaften der Metaboliten von 1,2-diphenyl-3,5-dioxo-4-n-butyl-pyrazolidin. Arzneimittel-Forsch. *10:* 129—33.

Yii, T. F., J. J. Burns et alii, 1958: Phenylbutazone metabolites: Antirheumatic, sodium-retaining and uricosuric effects in man. J. Pharmacol. Exp. Ther. *123:* 63—69.

Address: *Københavns Tandlægehøjskole,*
Universitetsparken 4,
København Ø, Denmark