A CONTROLLED TRIAL OF GLIFANAN AND OMNOPON IN POSTOPERATIVE PAIN*

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Although Glifanan has been available in South Africa for two years, no well-controlled clinical evaluations have been reported in this country. It was therefore decided to conduct an investigation into the efficacy of Glifanan using Omnopon 20 mg as the comparative drug. Chemically, Glifanan is 7-chlor-4-(o-(2,3-dihydroxy-propoxy-carbonyl) anilino) quinoline, a synthetic compound related to the quinoline group of antimalarial drugs. In animal tests it was found to have an analgesic potency 5 - 10 times greater than that of aspirin.[1] Anti-inflammatory and antipyretic properties were also demonstrated, but these were not as marked as the analgesic property. Initial clinical evaluations have also demonstrated marked analgesic potency.[2-28]

TRIAL DESIGN

Pathological pain is acknowledged to be the best yardstick for the measurement of analgesic effect.[29] In particular, postoperative pain, subjectively assessed, has given accurate and reproducible results. Excellent patient discernment between differing degrees of analgesia was obtained.[30-32] The investigation reported here involved postoperative pain in gynaecological and obstetric patients. The trial was a double-blind cross-over study. The trial medications were administered 6-hourly and the order of administration was randomized throughout. The study consisted essentially of two consecutive phases:

Phase 1. During the first 24 hours postoperatively Glifanan 500 mg in suppository form was compared with Omnopon 20 mg by injection.

Phase 2. During the subsequent 12 hours Glifanan 200 mg in capsule form was compared with Omnopon 20 mg by injection. Subjective pain assessment was made at the time of each drug administration and at hourly intervals for the next 5 hours.

In order to permit statistical evaluation of the results, pain was classified and scored according to principles suggested by Keele.[33] The classification and scores were as follows:

Severe pain	3
Moderate pain	2
Mild pain	1
No pain	0

The score at each hourly assessment was subtracted from the score at the time of administration. The 5 such values obtained were added to give a pain relief score for each dose.

*Date received: 2 October 1970.

In order to preserve the double-blind character of the study, each active suppository was given with a placebo injection and each active injection was given with a placebo suppository. In the second phase each active capsule was given with a placebo injection, and each active injection with a placebo capsule. The Glifanan in phase 2 was prepared in capsule form in order to facilitate the production of double-blind material.

In the trial, provision was made for the use of a 'back-up' analgesic if analgesia was not produced within one hour, and all such administrations were recorded. Various 'back-up' drugs were used, but pethidine 100 mg was used for the majority of patients. Effects other than the relief of pain were also monitored over the 6-hour period following each dose.

RESULTS

One hundred and eighty-one patients were admitted to the trial. They were suffering from moderate pain following the operations shown in Table I. The results are presented in two sections corresponding to the two phases of the trial:

TABLE I. SURGICAL PROCEDURES

Operation	*No. of patients*
Abdominal hysterectomy	60
Caesarean section	33
Vaginal hysterectomy	24
Others*	64
Total	181

*These operations included 34 salpingectomies, 3 salpingo-oophorectomies, 4 ovarian cystectomies, 1 oophorectomy, 6 myomectomies, 1 hysterotomy, 8 laparotomies, 6 vaginal repairs and 1 ventrisuspension.

Phase 1: Glifanan in Suppository Form vs. Omnopon Injection

A total of 609 dosage records was suitable for analysis, the principal reason for 'drop-out' being insufficient severity of pain. Table II shows the analysis of mean pain relief scores following the administration of each trial drug. Significantly higher pain relief scores were obtained following Omnopon injection than following Glifanan suppository for doses 1, 2, and 3. For dose 4 no significant difference emerged.

Table III shows the number of extra analgesics required following the administration of each trial analgesic. Overall, 64 doses of extra analgesics were administered following Glifanan suppository and 23 such doses following the

TABLE II. ANALYSIS OF MEAN PAIN RELIEF SCORES FOR OMNOPON INJECTION AND GLIFANAN SUPPOSITORY

	Mean pain relief score		*Difference between means*	*t*	*d.f.*	*Significance*
	Glifanan suppository	*Omnopon injection*				
Dose 1	3·39	5·86	2·57	4·108	168	s ($p<0·001$)
Dose 2	4·67	5·98	1·31	2·127	152	s ($0·025<p<0·05$)
Dose 3	4·52	5·70	1·18	2·638	156	s ($0·005<p<0·01$)
Dose 4	3·56	4·89	1·33	1·891	125	n.s. ($0·05<p<0·1$)

TABLE III. EXTRA ANALGESICS—PHASE 1

	Glifanan suppository	*Omnopon injection*
Trial doses followed by extra analgesics	64	23
Trial doses not followed by extra analgesics	237	285

administration of Omnopon. This difference is statistically significant (χ^2 = 26·7, 1 d.f., $p<0·001$).

Table IV shows the incidence, type and distribution of side-effects during phase 1.

TABLE IV. SIDE-EFFECTS—PHASE 1

	Glifanan suppository only	*Omnopon injection only*	*Glifanan suppository and Omnopon injection*	*Total*
No. of patients reporting side-effects	17	25	26	68
Side-effects				
Nausea	14	9	16	39
Vomiting	13	9	7	29
Dizziness	7	10	5	22
Headache	3	2	2	7
Sweating	1	2	2	5
Others	3*	6†	5‡	14
Total	41	38	37	116

*These side-effects included palpitations in 1 patient, rash on arm (1), abdominal cramps (1).
†These side-effects included mild hypotension (3), jaundice (1), rash at injection site (1), pain at injection site (1).
‡These side-effects included mild hypotension (1), light-headedness (1), hiccough (1), rash (1), shivering (1).

Phase 2: Glifanan in Capsule Form vs. Omnopon Injection

One hundred and sixty-two patients were given both trial drugs. Of these, 85 patients received Glifanan followed by Omnopon and the remaining 77 Omnopon followed by Glifanan. A further 3 patients received Glifanan only and 9 Omnopon only.

A total of 246 dosage records was available for analysis (Table V). Again the principal reason for 'drop-out' was insufficient severity of pain. There was no significant difference in the mean initial pain scores of the two treatment groups.

TABLE V. DISTRIBUTION OF ANALYSABLE RECORDS—PHASE 2

Drugs received	*No. of patients*	*No. of analysable dosage records*
Glifanan followed by Omnopon	85	127
Omnopon followed by Glifanan	77	114
Glifanan only	3	2
Omnopon only	9	3
None	7	—
Total	181	246

The mean pain relief scores following Omnopon injection and oral Glifanan showed no statistically significant difference (Table VI).

TABLE VII. EXTRA ANALGESICS—PHASE 2

	Oral Glifanan	*Omnopon injection*
Trial doses followed by extra analgesics	7	6
Trial doses not followed by extra analgesics	127	109

Table VII shows the number of extra analgesics required following the administration of each trial analgesic. The difference is not statistically significant.

TABLE VIII. SIDE-EFFECTS—PHASE 2

	Glifanan capsule only	*Omnopon injection only*	*Glifanan capsule and Omnopon injection*	*Total*
No. of patients reporting side-effects	10	14	5	29
Side-effects				
Nausea	3	9	1	13
Dizziness	2	7	1	10
Vomiting	2	4	2	8
Headache	2	2	—	4
Others	3*	3†	2‡	8
Total	12	25	6	43

*These side-effects included itchiness (1), prickly rash (1), sore throat (1) (probably intubation difficulty).
†These side-effects included itchiness (2), rash (1).
‡These side-effects included sweating (1), mild hypotension (1).

Table VIII shows the incidence, type and distribution of side-effects during phase 2.

DISCUSSION

The main object of this investigation was the comparative evaluation of oral Glifanan and Omnopon injection in order to determine the place of Glifanan in the analgesic spectrum.

The results obtained indicate that a high level of analgesia is possible with 200 mg of Glifanan by mouth. The pain relief was found to be comparable to that obtained from Omnopon injection 20 mg. On the evidence presented it would appear that Glifanan could be a useful means of minimizing the therapeutic gap between analgesics of the aspirin type and the narcotic analgesics.

As postoperative patients were the subject of the study it was necessary to wait until they could tolerate oral medication. Glifanan was, however, made available in the form of suppositories and it was therefore decided to use the first 24 hours in a second experiment comparing Glifanan suppositories with Omnopon. Glifanan in this form was found to be less effective than Omnopon, but

TABLE VI. ANALYSIS OF MEAN PAIN RELIEF SCORES FOR OMNOPON INJECTION AND ORAL GLIFANAN

	Mean pain relief score		*Difference between means*	*t*	*d.f.*	*Significance*
	Omnopon injection	*Glifanan capsules*				
Dose 1	5·80	4·87	0·93	1·402	132	n.s. ($0·1<p<0·2$)
Dose 2	5·55	5·07	0·48	0·777	113	n.s. ($0·4<p<0·5$)

a considerable degree of analgesia was nevertheless obtained.

In a subsequent investigation elsewhere[34] the blood levels obtained following rectal Glifanan were found to be lower than those obtained following oral Glifanan, and this could account for the therapeutic difference observed. It was gratifying to find that the method used was sufficiently sensitive to establish these differences and this must endorse the findings in the main phase of the trial.

Side-effects noted throughout were of a minor nature and it is difficult to draw any conclusions regarding these since they all occurred within 36 hours of a major operation.

SUMMARY

A double-blind cross-over technique was used to evaluate the pain relief obtained postoperatively in gynaecological and obstetric patients following the administration of Omnopon injection, Glifanan suppositories and Glifanan capsules. Pain was classified hourly by the patient and pain relief scores for each test administration were calculated and statistically analysed. These showed no statistically significant difference following Omnopon injection 20 mg and Glifanan capsules 200 mg. Pain relief scores following Omnopon injection 20 mg were significantly higher than those following Glifanan suppositories 500 mg.

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