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DIFLUNISAL: EFFICACY IN POSTOPERATIVE PAIN

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1 Seven hundred and forty patients complaining of pain after oral or orthopaedic surgery or episiotomy were studied in five single dose or short-term double-blind, controlled, randomized studies comparing efficacy and safety of diflunisal with that of acetylsalicylic acid, glafenin or placebo.

2 Diflunisal was found to be effective in relieving postoperative pain in 75–85% of patients. A twice day dosage schedule seems to be clinically adequate, 375 mg twice daily proving to be equally effective as glafenin 200 mg three times daily. No serious drug-related clinical or laboratory adverse experiences were encountered in any of the five studies.

Introduction

Pain in any form, no matter to what extent the patient has become either preconditioned or accustomed, should be alleviated whenever possible; and the description of pain as 'inevitable' or even 'normal' when it is preventable, is to be deplored. Postoperative pain is an instance of this attitude that could bear improvement.

Quite recently in the *British Medical Journal* (18 September, 1976), a leading article expressed concern that postoperative pain has not aroused sufficient interest. A statement made in this article can profitably be quoted here: 'Both doctors and nurses are afraid of inducing addiction and, like many patients, have too complacently accepted pain as an inevitable consequence of surgery.'

A considerable gap still exists between the parenterally administered potent analgesics with their accompanying disadvantages and dangers, and the presently available oral analgesics. Diflunisal, because of its long duration of analgesic action, seems to be an attractive candidate to fill the gap between the potent parenteral analgesics and the less potent, relatively short-term oral analgesics. Encouraging results have been obtained in clinical studies using single and multiple doses of diflunisal in patients with moderate or severe pain after a surgical intervention.

Single dose studies

There have been double-blind studies comparing three dose levels of diflunisal with acetylsalicylic acid (ASA) (600 mg) and placebo. The first study (P. De Vroey, personal communication), involving 161 patients, was carried out on women who had had an otherwise uncomplicated delivery within 48 h of the start of the study and who had moderate to severe pain secondary to an episiotomy. Of these patients, 156 met all the protocol criteria and were evaluated for efficacy. The distribution among the treatment groups and the degree of pain present before the treatment, as expressed by pain scores of 0 to 3 are shown in Table 1. The patients were questioned before and at 1-h intervals for 6 h after administration of a single

Table 1 Single dose postepisiotomy pain*

Treatment group	*Pain score* 0	1	2	3	*Total number of patients*
Diflunisal 125 mg	0	0	17	16	33
Diflunisal 250 mg	0	0	20	10	30
Diflunisal 500 mg	0	0	18	12	30
ASA 600 mg	0	0	14	18	32
Placebo	0	0	12	19	31
Total	0	0	81	75	156

* Distribution of patients by treatment group and degree of pain at hour 0 (pretreatment).
Pain score: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

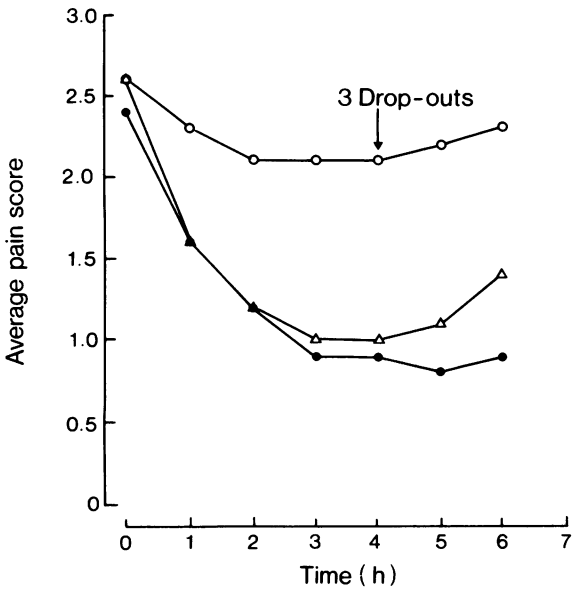

Figure 1 Single dose post-episiotomy pain. ○, Placebo ($n=31$); △, ASA 600 mg ($n=32$); 1 drop-out at hour 3 during 6 h follow-up); ●, diflunisal 500 mg ($n=30$). Pain score coded as in Table 1.

Table 2 Single dose postepisiotomy pain*

		ASA	*Diflunisal*		
Hour	*Placebo*	*600 mg*	*125 mg*	*250 mg*	*500 mg*
0	2.6	2.6	2.5	2.3	2.4
1	2.3	1.6	1.8	1.7	1.6
2	2.1	1.2	1.5	1.5	1.2
3	2.1	1.0	1.3	1.4	0.9
4	2.1	1.0	1.4	1.3	0.9
5	2.1	1.1	1.4	1.3	0.8
6	2.3	1.4	1.5	1.3	0.9

* Average pain score for each treatment group over 6 hours.

dose of the test medication to each treatment group, and the degree of pain noted.

Three patients in the placebo group were withdrawn from the study at hour 4 because of severe pain and one patient in the ASA group was withdrawn at hour 3 for reasons unrelated to pain or the drug. The hour-to-hour results obtained throughout the 6-h period, expressed as mean pain scores, are shown in Table 2. In Figure 1, the data of the placebo group, the ASA group and the diflunisal 500 mg group are graphically presented.

The other single dose study (W.S. Honig, personal communication) was carried out in 150 patients aged 21–65 yr of either sex, who had moderate or severe pain on the morning of the day after meniscectomy. Three patients were excluded from the efficacy analysis because of protocol violations. The distribution of the remaining 147 patients among the five treatment groups and the degree of pain present as expressed by pain scores of 0 to 3, are shown in Table 3 (pretreatment) and Table 4 (8 h). There were 30 dropouts, of which 28 were due to insufficient pain relief, and two for other reasons not related to pain or the drug.

The 28 dropouts were divided among the groups as follows: diflunisal 125 mg group, 5; diflunisal 250 mg group, 4; diflunisal 500 mg group, 4; ASA 600 mg group, 5; Placebo group, 10.

The hour-to-hour results obtained throughout the 8-h period, expressed as mean pain scores, are shown in Table 6. Figure 2 illustrates graphically the results in the diflunisal 500 mg group, the ASA group, and the placebo group.

One could argue that presentation of the data in Figures 1 and 2 is incorrect, since a pain score of 3 (severe pain) is not mathematically three times more severe as a pain score of 1 (mild pain). In figure 3 an attempt has been made to illustrate the data in a more acceptable way by plotting the approximate percentage of 'responders' over time. 'Response' is defined as a decrease in pain score of 1 degree or more. Figure 3 clearly illustrates the longer duration of analgesic action after a dose of diflunisal 500 mg

Table 3 Single dose postmeniscectomy pain*

	Pain score				*Total number*
Treatment group	*0*	*1*	*2*	*3*	*of patients*
Diflunisal 125 mg	0	0	20	9	29
Diflunisal 250 mg	0	0	16	12	28
Diflunisal 500 mg	0	0	24	7	31
ASA 600 mg	0	0	22	8	30
Placebo	0	0	19	10	29
Total	0	0	101	46	147

* Distribution of patients by treatment group and degree of pain at hour 0 (pretreatment). Pain score coded as in Table 1.

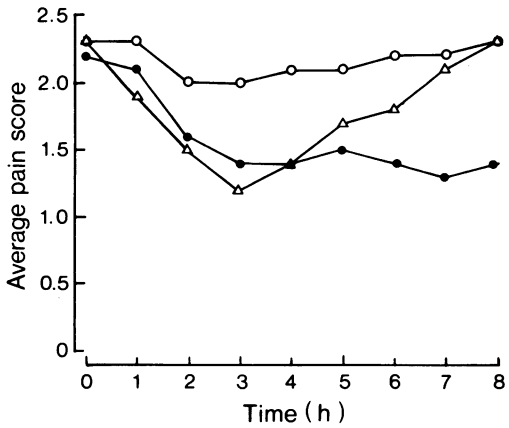

Figure 2 Post-meniscectomy pain. ○, Placebo ($n=29$; 11 drop-outs); △, ASA 600 mg ($n=30$; 5 drop-outs); ●, diflunisal ($n=31$; 4 drop-outs).

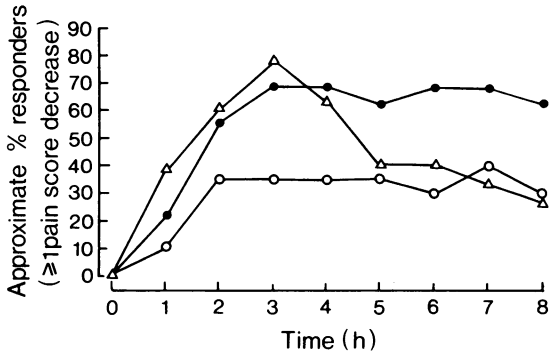

Figure 3 Post-menisectomy pain. ●, Diflunisal ($n=31$); ○, placebo ($n=29$); △, ASA ($n=30$).

orally compared with a dose of ASA 600 mg orally. Figure 3 also shows, however, that the onset of analgesic effect is somewhat slower for diflunisal than for ASA (see also Table 5).

The results obtained in these two double-blind, single dose studies show that: diflunisal, when orally administered at doses of 125 mg, 250 mg and 500 mg, is an effective analgesic; that diflunisal's duration of analgesic action extends over a period of at least 8 h; that diflunisal's onset of action seems to be somewhat slower than that of a standard dose of ASA; and that the optimal starting dose of diflunisal is probably 500 mg.

Multiple dose studies

The clinical evaluation of diflunisal has also included short-term (up to 7 d) multiple doses studies intended to demonstrate comparative efficacy in orthopaedic postoperative pain and in dental pain after oral surgery.

Dental study

This multiclinic study (K. Ackermann, C.A. Merkx & J. Kolsen Petersen, personal communication) of a double-blind, controlled, randomized design was carried out by three independent investigators using the same protocol. The analgesic efficacy of diflunisal 500 mg was compared with placebo response in patients suffering from pain after the surgical removal of impacted teeth. The dose could be repeated on demand twice only, provided that a minimum interval of 6 h was maintained between doses. The administration of a standardized additional analgesic was permitted in case of unbearable pain not relieved by the test medication.

One hundred and eighty patients of both sexes (15–60 yr) were admitted to this study, all suffering from moderate to severe postoperative pain of at least one hour's standing. After being randomly allocated to either the diflunisal or the placebo group, each patient

Table 4 Single dose postmeniscectomy pain*

Treatment group	*Pain score* 0	1	2	3	*Total number of patients*
Diflunisal 125 mg	2	11	6	4	23
Diflunisal 250 mg	3	7	9	5	24
Diflunisal 500 mg	8	10	5	4	27
ASA 600 mg	0	6	10	9	25
Placebo	2	5	5	6	18
Total	15	39	35	28	117

* Distribution of patients by treatment group and degree of pain at hour 8. Pain score coded as in Table 1.

Table 5 Single dose postmeniscectomy pain

Hour	Placebo	ASA 600 mg	Diflunisal 125 mg	Diflunisal 250 mg	Diflunisal 500 mg
0	2.3	2.3	2.3	2.4	2.2
1	2.3	1.9	2.2	2.2	2.1
2	2.0	1.5	1.9	2.0	1.6
3	2.0	1.2	1.7	1.8	1.4
4	2.1	1.4	1.6	1.8	1.4
5	2.1	1.2	1.3	1.5	1.5
6	2.2	1.8	1.3	1.6	1.4
7	2.2	2.1	1.4	1.5	1.3
8	2.3	2.3	1.5	1.7	1.4

* Average pain score for each treatment group over 8 hours.

Table 6 Dental pain

	Number of patients	
	Diflunisal	Placebo
Patients taking all three doses of test medication, but no other analgesics	32	26
Patients taking less than three doses of test medication because of adequate pain relief	40*	18
Patients taking test medication plus additional analgesics	4	35**
Total	76	79

At post-treatment the diflunisal group had significantly lower (=better) pain scores than the placebo group ($P < 0.001$).
* Proportion of patients significantly higher in diflunisal group than in the placebo group ($P < 0.001$).
** Proportion of patients significantly higher in placebo group than in the diflunisal group ($P < 0.001$).

received the test medication. The second dose if required, was permitted at bedtime or during the night, and the third if necessary could be taken after breakfast. The 6-h interval between doses would be respected at all times.

Two patients from each group took no medication and were therefore excluded from analysis. Also excluded from analysis were 12 diflunisal patients and 8 placebo patients. All of them violated the protocol since their initial pain was less than 'moderate'.

Thus, 76 patients in the diflunisal group and 79 in the placebo group were included in the efficacy analysis which was based on the measurement of spontaneous pain, the patient's overall evaluation of response to treatment and the investigator's overall evaluation of treatment efficacy.

Examination of the data obtained in this study, pooled across clinics, showed a statistically significant difference in favour of diflunisal in each and every parameter used in determining efficacy of treatment. The proportion of patients requiring additional analgesics for the relief of pain significantly favoured diflunisal (Table 6). Table 7 shows the pretreatment and the post-treatment pain scores and the distribution of patients in both treatment groups.

Treatment was considered to be a 'success' in those cases in which the investigator's overall evaluation of efficacy was excellent or good, no additional analgesics were required, and adverse reactions were either absent or acceptable. The success' rate in the three pooled studies is shown in Table 8.

This study shows that diflunisal is an effective analgesic in 84% of patients suffering from moderate or severe pain after oral surgery, whereas placebo gave a similar result in only 28% of patients.

Orthopaedic postoperative pain

Under this heading are included two studies, one of which is concerned with pain after meniscectomy and one with pain after various orthopaedic procedures.

Table 7 Dental pain scores

Initial score	Diflunisal post-treatment score					Total	Placebo post-treatment score					Total
	4	3	2	1	0		4	3	2	1	0	
4	0	0	1	7	8	16	2	2	5	10	3	22*
3	0	1	1	13	25	40	0	1	8	10	8	27
2	0	0	0	3	17	20	0	0	0	13	16	29
Total	0	1	2	23	50	76	2	3	13	33	27	78

Pain score coded as in Table 1.
* One patient (allocation number 154) came 24 h late and has been excluded from this analysis.

Pain after meniscectomy. This double-blind, completely randomized study (W.J. Honig, personal communication) compared the effect of two dosages of diflunisal 375 mg twice daily and 500 mg twice daily, compared with placebo in the 7 d postoperative period after knee surgery for meniscectomy in 120 patients.

Patients entering this study complained of moderate to severe pain on the morning of the day after surgery, and were randomly allocated to one of three treatment groups, each group consisting of 40 patients. All patients were examined at least once per day, and their body temperature, tenderness, spontaneous pain, pain on movement, and swelling of the joint recorded. The treatment was judged to be a 'success' when the patient completed the study period, the efficacy was good or excellent and no other analgesic was taken, and adverse reactions were either absent or acceptable.

The results obtained from this study indicated that: the patient's and investigator's overall opinion of efficacy of treatment, was consistently in favour of both diflunisal groups; and that the overall success rate was significantly in favour of the diflunisal groups ($P < 0.005$), being recorded as 70–75% in the diflunisal groups compared with 38% in the placebo groups.

No consistent difference in efficacy was found between the two dosages of diflunisal. It seems, therefore, that diflunisal at a dose of 375 mg twice daily or 500 mg twice daily, is an effective analgesic for the control of pain after meniscectomy. These findings have since been confirmed in another similar study (A.R. Kreuzen, personal communication).

Pain after orthopaedic surgery

Three investigators (J. Debeyré, O.W. Mohing, M.H. Ruidisch, personal communication), using the same protocol, carried out a multiclinic, double-blind, completely randomized study of diflunisal 375 mg twice daily, compared with glafenine 200 mg three times daily over a period of 5 d in postoperative pain after various orthopaedic procedures. The objective was to compare the analgesic efficacy of both compounds.

One hundred and twenty patients were admitted to the study and randomly allocated to each treatment group. One patient in the diflunisal group was not included in the efficacy analysis because of a protocol violation. Nine patients did not complete the course of treatment, six because of ineffective treatment (four in the diflunisal group and two in the glafenine group), and two because of adverse reactions (both in the glafenine group).

Patients who complained of moderate to severe pain on the morning after surgery were admitted to the study, and randomly allocated to one of the two treatment groups. Each group contained 60 patients. Any patient who required additional analgesics during the study period was considered to be a treatment failure.

All patients were examined at least once per day for all parameters: body temperature; joint swelling; tenderness; investigator's overall evaluation; patient's rating of spontaneous pain, and patient's opinion of overall effectiveness. Success rates defined in previous studies were also analyzed statistically. Approximately 75% of patients in each group showed excellent to good results and no statistically significant difference between groups could be found in any of the efficacy parameters measured, including the success rate of treatment.

Diflunisal at 375 mg twice daily was found to be an effective analgesic in postoperative pain after orthopaedic procedures, and was equally effective as glafenine 200 mg three times daily.

Table 8 Success rate in three pooled studies

	Diflunisal		*Placebo*	
	Patients	*%*	*Patients*	*%*
Success	64	86	22	28
Failure	12	16	57	72
Total	76	100	79	100

Conclusions

In all the above studies, diflunisal at various dose levels studied has consistently proved its effectiveness as an analgesic in 75–85% of patients suffering from postoperative pain. A twice daily dosage schedule seems to be clinically adequate. The initial dose should be 500 mg followed by 250–375 mg twice daily.

Diflunisal was shown to be comparable in efficacy to glafenine. No serious, drug-related clinical or laboratory adverse experiences were noted in any of the five studies discussed.

There are many more studies being carried out with diflunisal and even more will follow. At present, on the evidence already available, diflunisal seems to be able to contribute towards helping the patient who suffers, perhaps unnecessarily, from postoperative pain.

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