CLINICAL EFFICACY OF MILD ANALGESICS IN PAIN FOLLOWING GYNAECOLOGICAL OR DENTAL SURGERY: REPORT ON MULTICENTRE STUDIES

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- 1 Dipyrone 1.0 g, paracetamol 1.0 g and placebo were compared in a double-blind parallel group study in patients with episiotomy pain.
- 2 Patients were stratified according to severity of initial pain (severe or moderate) and the three treatments were randomized for each of these two groups.
- 3 Two-hundred and sixty-four patients entered the study: five patients were excluded from analysis; 127 patients had 'severe' pain, 132 'moderate' pain.
- 4 Both drugs were more effective than placebo, and dipyrone was significantly more effective than paracetamol, particularly where initial pain was severe.
- 5 The efficacy of dipyrone 1.0 g was compared with paracetamol 1.0 g in relieving pain after tooth extraction.
- 6 Ninety patients entered the study and 87 were analyzed without stratification according to initial pain severity.
- 7 Dipyrone was consistently and significantly more effective than paracetamol at every assessment.

Introduction

THE physiopathology of pain and the mechanism of action of some analgesics are better understood since the discovery of prostaglandins (Vane, 1971), and enkephalins and endorphins (Hughes *et al.*, 1978). This has stimulated much interest in both experimental and spontaneous pain. Many analgesics have, however, been available for several decades, although they have not been evaluated according to modern methodology. Dipyrone is one of these compounds, and we assessed its efficacy in relieving episiotomy and dental surgery pain, in comparison with paracetamol. In the first study a negative control, placebo, was also used.

Methods

Episiotomy pain

Dipyrone 1.0 g, paracetamol 1.0 g and placebo were compared in a single-dose, randomized, double-blind parallel group study. Patients were aged more than

16.0 yr, had undergone episiotomy, and had moderate or severe pain within the following 24 hours. The nature of the study was explained, and patients consented freely to participate.

Patients were excluded if they had a history of sensitization to paracetamol or pyrazolones, allergic diathesis, alcoholism, drug abuse, psychiatric disturbance, gastrointestinal bleeding, peptic ulcer, known severe hepatic, or renal disease or other obstetric intervention.

Drugs were administered with a glass of water and no food was permitted in the preceding or subsequent 30 minutes. No other analgesics or sedatives were permitted between the episiotomy (performed with xylocaine anaesthesia) and the end of the 6-h assessment period unless there was no pain relief 2 h after administration of the test drug. If this occurred, patients were regarded as 'drug failures'.

Evaluations of pain were made by the same investigator before and 30 min after drug administration and at hourly intervals for 6 hours.

Pain was assessed on a five-point scale as follows: 0, none; 1, mild; 2, moderate; 3, severe; 4, very severe. If patients were asleep at any assessment there was no evaluation. Adverse effects of which patients spontaneously complained were recorded at each assessment.

Pain after dental surgery

In this study there was no placebo comparison. Eligible patients attended either of two dental clinics for the extraction of impacted third molar teeth and had to complain afterwards of moderate or severe pain to participate. The treatment groups received either dipyrone 1.0 g or paracetamol 1.0 g according to a random code.

The administration of drug, the frequency, duration and assessment of pain before and after treatment, the exclusion criteria and the method of recording adverse reactions were similar to those described in the first protocol.

Results

Episiotomy

Two hundred and sixty-four patients entered the study, 66 in each of four centres; 259 completed the study; 132 had initially moderate, and 127 severe pain. Five patients received additional medication at 2 h, three in the paracetamol group, and two who received placebo. A breakdown of the patients according to age, weight, height and initial intensity of pain is shown in Table 1. The treatment groups were clearly homogeneous.

Patients were stratified according to their initial pain level, and treatment was then randomized. This ensured that treatment groups were of comparable size at both pain levels (Table 2).

The majority of mothers were primiparous (85%) and the distribution according to parity was also homogeneous (Table 3).

Mild adverse effects were reported in all treatment groups, namely, dizziness, nausea, vertigo, sweating, headache, gastric upset and increased vaginal bleeding. These were slightly less common in the placebo group.

Four patients in the placebo group and one in the paracetamol group were asleep during some of the assessments, and are excluded from the time-curve pain intensity calculation. The mean values of pain intensity are shown in Table 4. Dipyrone was significantly more effective than paracetamol at every assessment up to 4 h, in relieving severe pain (Figure 1).

Paracetamol was significantly more effective than placebo. These results were consistent for all centres for severe pain, and three centres for moderate pain.

Table 1 Distribution of patients in treatment groups according to age, weight, height, and stratification according to intensity of initial episiotomy pain

Moderate pain			
	Dipyrone (n = 44)	Paracetamol (n = 45)	Placebo (n = 43)
Age	22.4 (17–27)	22.0 (17–29)	21.1 (16–27)
Weight (kg)	64.5 (46–80)	65.4 (53–78)	62.8 (50–72)
Height (cm)	154.1 (148–162)	154.3 (146–164)	153.1 (146–164)
Severe pain			
	Dipyrone (n = 44)	Paracetamol (n = 41)	Placebo (n = 42)
Age	22.3 (16–33)	21.4 (16–27)	20.8 (16–26)
Weight (kg)	65.6 (50–79)	64.3 (48–76)	65.2 (50–74)
Height (cm)	154.5 (143–163)	153.0 (143–164)	153.3 (147–159)

Numbers in parentheses = range.

Table 2 Distribution of patients in treatment groups in each of four centres (C1–C4) and stratified by intensity of initial episiotomy pain

Moderate pain (n = 132)					
	C1	C2	C3	C4	Total
Dipyrone	11	11	11	11	44
Paracetamol	11	12	11	11	45
Placebo	11	11	11	10	43
Total	33	34	33	32	132
Severe pain (n = 127)					
Dipyrone	11	11	11	11	44
Paracetamol	9	10	11	11	41
Placebo	10	11	11	10	42
Total	30	32	33	32	127
Total	63	66	66	64	259

Pain after dental surgery

Ninety patients entered the study: 48 in one centre, 42 in another. Forty-five patients received dipyrone and 45 paracetamol. Three patients in the paracetamol group required additional analgesia 2 h after the test drug. The distribution of patients

Table 3 Distribution of patients according to parity in each treatment group after stratification for intensity of initial episiotomy pain

<i>Moderate pain</i>			
	<i>I</i>	<i>Parity II</i>	<i>III</i>
Dipyrone	34	6	4
Paracetamol	38	5	2
Placebo	36	6	1
Total	108	17	7
<i>Severe pain</i>			
Dipyrone	39	4	1
Paracetamol	38	2	2
Placebo	34	7	2
Total	111	13	5
Total	219	30	12

Table 4 Mean pain intensity scores for 6 h after medication, stratified by severity of initial pain

<i>Moderate pain</i>			
<i>Time (h)</i>	<i>Dipyrone (n = 44)</i>	<i>Paracetamol (n = 45)</i>	<i>Placebo (n = 43)</i>
0	2.00	2.00	2.00
0.5	0.57	1.02	1.88
1	0.32	0.60	1.81
2	0.23	0.40	1.77
3	0.20	0.33	1.70
4	0.27	0.53	1.47
5	0.41	0.89	1.07
6	0.57	0.87	0.93
<i>Severe pain</i>			
<i>Time (h)</i>	<i>Dipyrone (n = 44)</i>	<i>Paracetamol (n = 41)</i>	<i>Placebo (n = 42)</i>
0	3.43	3.39	3.21
0.5	1.75	2.32	3.17†
1	0.95	1.65*	2.78‡
2	0.64	1.43*	2.66§
3	0.57	1.32	2.32¶
4	0.66	1.34	2.08*
5	1.05	1.37	1.79
6	1.11	1.37	1.40

Number of patients: *40; †41; ‡36; §35; ¶37.

according to age, weight, sex and height is shown in Table 5. As only 10 of the 87 patients who were analyzed further had severe pain, they were all analyzed together. Table 6 shows the number of patients in each treatment group analyzed by time and pain intensity. The mean pain intensity level at each assessment is shown in Table 7.

Figure 1 Total means of pain intensity in severe cases (post-episiotomy) during 6 h after drug administration. Significance levels: dipyrone/paracetamol *** <0.001 ; ** <0.01 ; NS, not significant. ○, Dipyrone; ■, paracetamol; □, placebo.**Table 5** Pain after dental surgery.

	<i>Dipyrone (n = 45)</i>	<i>Paracetamol (n = 45)</i>
Sex Male	11	18
Female	34	27
Age	26.4 (7-75)	29.6 (12-68)
Weight (kg)	57.5 (28-83)	61.4 (42-85)
Height (cm)	160.6 (115-190)	164.2 (145-197)

Numbers in parentheses = range.

The results were the same in both centres, dipyrone being significantly more effective than paracetamol throughout the study period (Figure 2). In this study throughout the study period (Figure 2). All the patients treated with dipyrone achieved pain relief (Figure 3).

Discussion

Drugs which relieve pain can be assessed adequately only in double-blind studies, ideally in comparison

Table 6 Number of patients and mean pain intensity for 6 h after medication (dental surgery)

<i>Dipyrone (n = 45)</i>					
<i>Time (h)</i>	<i>None</i>	<i>Light</i>	<i>Moderate</i>	<i>Severe</i>	<i>Asleep</i>
0			40	5	
0.5	18	16	11	0	0
1	41	4	0	0	0
2	45	0	0	0	0
3	43	0	0	0	2
4	42	1	0	0	2
5	37	3	0	0	5
6	34	4	0	0	7

<i>Paracetamol (n = 42)</i>					
<i>Time (h)</i>	<i>None</i>	<i>Light</i>	<i>Moderate</i>	<i>Severe</i>	<i>Asleep</i>
0			37	5	
0.5	8	13	17	4	0
1	23	13	2	4	0
2	35	4	0	3	0
3	36	4	1	1	0
4	26	15	1	0	0
5	16	19	5	0	2
6	17	15	8	0	2

Table 7 Total mean pain intensity scores (dental surgery)

<i>Moderate + severe pain</i>		
<i>Time (h)</i>	<i>Dipyrone (n = 45)</i>	<i>Paracetamol (n = 42)</i>
0	2.11	2.12
0.5	0.84	1.40
1	0.09	0.69
2	0.00	0.31
3	0.00*	0.21
4	0.02*	0.40
5	0.07*	0.72*
6	0.11*	0.77*

* Number of patients was reduced as some fell asleep.

with positive and negative controls. The ethical problem of administering a placebo to patients suffering from pain is surmountable providing a mechanism exists to ensure patients with inadequate relief can obtain further treatment early in the study period.

The response of patients to analgesics as assessed by the same methods but in different hands and in a different environment may not be identical. In the study in episiotomy pain four of the centres produced similar results in moderate pain and three in severe pain. Both drugs were consistently more effective than placebo.

Results of both studies corroborate the experience of general clinical practice regarding the relative efficacy of the two drugs. Dipyrone consistently

Figure 2 Total mean pain intensity scores (dental surgery) during 6 h after drug administration. Significance levels: *** <0.001 ; ** <0.01 . O, Dipyrone; ■, paracetamol. **Figure 3** Percentage of patients without pain after administration of dipyrone (O) or paracetamol (■) after dental surgery.

produced greater pain relief than paracetamol, particularly where initial pain was severe.

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