

# Open Labelled Evaluation of Injection Manyana™ (A Combination of Diclofenac + Pitofenone + Fenpiverinium) in Ureteric, Biliary and Intestinal Spasm - A Preliminary Report

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## ABSTRACT

To study the efficacy and safety of a parenteral formulation of 'Manyana™' (a combination of diclofenac + pitofenone + renpiverinium) in ureteric, biliary and intestinal colic, an open labelled study was conducted at two centres. A total of 206 patients were enrolled and evaluated for decrease in pain with time on a visual analogue scale. A statistically significant difference was observed in pain within 30 minutes of drug administration and the pain relief lasted for as long as 24 hours post dosing. The study shows definite synergism between the antispasmodics pitofenone and fenpiverinium with the NSAID -diclofenac, reducing the prostaglandin levels and also the spasm related to colic.

## INTRODUCTION

Acute abdominal pain presents a challenge, to the diagnostician and the therapist. Most obvious cases of acute abdomen may not require surgical intervention. Often the culprit is the mass of smooth muscle in the abdomen going in uncontrolled spasm. Colic is one of the most common causes of abdominal pain. Usually it is attributed to spasm of the intestinal, biliary or ureteric smooth muscles. Obstruction is the main cause of biliary and ureteric spasm but the patho-physiology of intestinal colic is not clear.

Pain and smooth muscle spasm feed on each other. Involved in the vicious cycle is the arachidonic acid cascade, which leads to the formation of large amounts of prostaglandins. These fatty acid derivatives, not only enhance the spasmogenic response of smooth muscles to other stimulants, but also sensitize the nerve endings to pain. Inhibition of the cascade is therefore central to the control of spasmodic pain of the abdomen. NSAIDs in addition to being analgesic, inhibit the formation of prostaglandins, and are the best agents to control colic'. Cholinergic, tryptaminergic and some less common systems also mediate smooth muscle contraction. Non specific smooth muscle relaxants as well as anticholinergic drugs therefore play a role in the management of colic.

In the past some formulations containing pitofenone hydrochloride (a non-specific smooth muscle relaxant), fenpiverinium bromide (an anticholinergic agent) have been widely used. 'Baralgan™' contained analgin as the analgesic in combination with (the two above named antispasmodics. Doubts raised over the safety of analgin, have led to its withdrawal, but the need for such combinations continues to be felt. Diclofenac sodium, an aryl acetic acid derivative, with potent analgesic, anti-inflammatory and antipyretic activity<sup>2</sup>, can safely replace analgin, and has been used to formulate 'Manyana™'.

A multicentric open labelled study was undertaken on 'Manyana' parenteral formulation in patients with intestinal, biliary or ureteric colic. The trial was designed to elucidate the onset, efficacy, duration of action and the safety of the formulation.

## PATIENTS AND METHODS

A total of 206 patients in the age range of 16-60 years who were suffering from intestinal, biliary or ureteric colic and willing to be admitted in the hospital for a minimum of 24 hours were included in the study. Patients who required immediate surgery for their underlying condition, suffering from ulcer disease, who had consumed antispasmodic medication 2 hours before reporting to the hospital or pregnant women were excluded from the study- Patient's informed consent was obtained.

Of the total patients enrolled 68 were suffering from intestinal colic, 45 from biliary colic and 93 from ureteric colic (Table 1).

After recording the history of the patient, they were clinically examined. All routine examinations considered appropriate by the investigators were conducted on the patients. The findings were recorded in the record sheets.

Out of 206 patients 146 patients had colic of less than 6 hours duration (Table 2).

Table 3 depicts history of past illness. A total of 114 patients did not have history of past illness.

**Table 1 - Diagnosis**

Diagnosis	Male		Female		Total
	CTR 1	CTR 2	CTR 1	CTR 2	
Intestinal colic	16	20	16	16	68
Biliary colic	15	3	16	11	45
Ureteric colic	24	27	20	22	93
Total	55	50	52	49	206

**Table 2 - Duration of Colic**

Duration in hours	Male	Female	Total
<4	41	31	72
4-6	33	41	74
6-12	22	18	40
12-24	6	7	13
>24	3	4	7
Total	105	101	206

**Table 3 - Duration of Illness**

Duration	Intestinal		Biliarv		Urclcric		Total
	CTR1	CTR2	CTR1	CTR2	CTR1	CTR2	
No history	19	31	12	6	14	32	114
1-4 months	4	3	4	3	11	9	34
4-6 months	3	0	9	2	12	3	29
6-12 months	5	0	4	2	5	1	17
>12 months	1	2	2	1	2	4	12
Total	32	36	31	14	44	44	206

These patients had other associating symptoms such as nausea (138), vomiting (53), radiating pain (89), haematuria (57), diarrhoea (39).

No abnormality on clinical examination was observed. Eighty-five per cent of patients had tachycardia. Abdominal examination was thoroughly done. Tenderness was present in 120 patients, rigidity was present in 26 patients. There was no other abnormality seen on clinical examination.

The test preparation injection 'Manyana' was administered in a dose of 1 ml (containing fempiverinium, pitofenone and diclofenac) intramuscularly after taking and recording the history and the findings of the clinical examination. Pain relief was graded using a 0-100mm Visual Analogue Scale.

An alternative antispasmodic or analgesic (narcotic/n on-narcotic) was administered to the patients, only if the patients did not respond to the test medication within 30 to 60 minutes after administration. These patients were considered as non-responders or treatment failures. and fresh patients did not replace them.

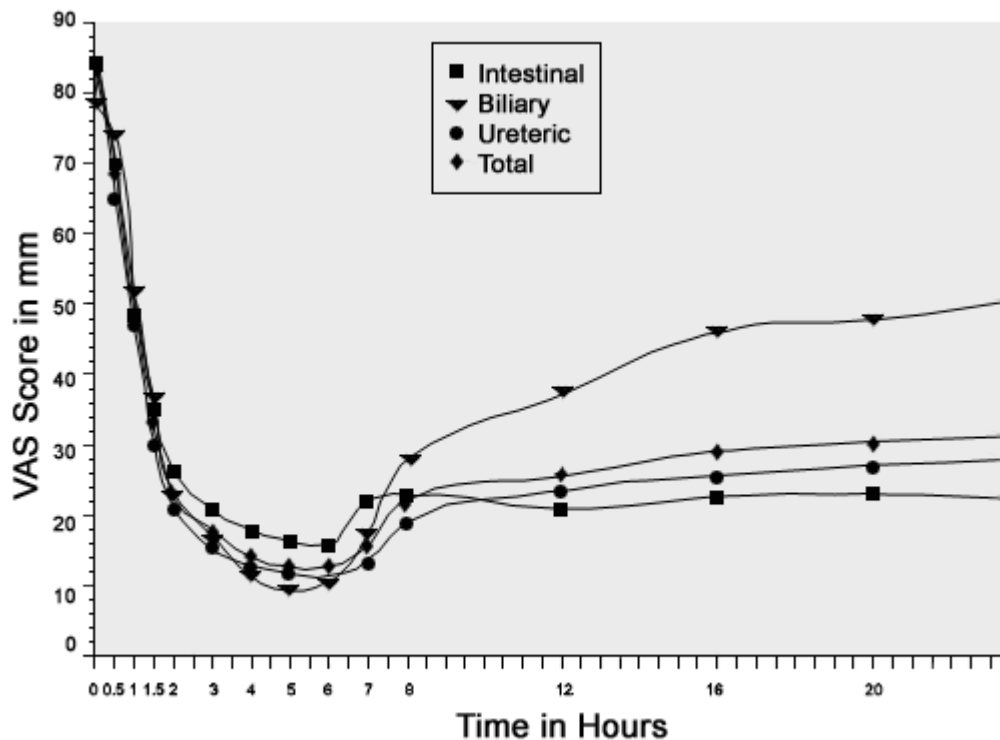


Fig 1: VAS Score in Intestinal, Biliary, Ureteric Colic and Total (0-24 Hours)

## OBSERVATIONS

Analysis of Visual Analogue Scale (VAS) scores from the patients depicted that the symptoms showed a rapid decline immediately following a dose of the test medication. The mean VAS score at 30 minutes showed statistically significant difference when compared to the basal VAS. Since the difference between VAS at basal and at 30 minutes was significant, the onset of action of the formulation is probably less than 30 minutes (Table 4).

Peak action of the medication, reflected by the nadir of the VAS score was observed at 4 to 6 hours in patients of each types of colic. After the nadir the VAS scores showed a rise- Appreciable amount of pain was reported at 12 hours post dose. and there was a gradual rise in the score till 24 hours (Fig 1).

There appears a difference in the reappearance of pain with time. Patients with biliary colic reported recurrence of pain after 8 to 12 hours and the VAS ratings were significantly higher than those of other patients.

Concomitant therapy (antidiarrhoeals, antibiotics, urinary antiseptics. etc) was taken by 14 patients having intestinal colic. 4 having biliary colic and 11 having ureteric colic. No side effects were seen which necessitated the withdrawal of the drug.

Time	Intestinal colic		Biliary colic		Ureteric colic		Total	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Basal	84.18	19.41	78.24	18.89	83.34	17.15	84.35	15.81
30 minutes	69.87*	30.65	73.77	25.04	65.04*	35.07	68.56*	36.68
60 minutes	48.4*	26.26	51.54*	22.64	47.3*	28.32	48.15*	32.21
90 minutes	35.3*	27.13	36.44*	19.86	30.0*	20.80	33.2*	24.31
2 hours	26.43*	25.21	22.49*	22.47	21.1*	25.17	23.15*	24.68
3 hours	21.0*	23.29	17.13*	20.75	15.5*	20.41	17.66*	21.66
4 hours	17.8*	19.87	11.54*	17.48	12.9*	18.61	14.16*	19.19
5 hours	16.45*	18.82	9.46*	17.36	11.8*	18.10	12.77*	18.54
6 hours	15.91*	18.78	10.63*	17.18	11.3*	17.59	12.66**	18.24
7 hours	22.19*	19.53	17.18*	18.56	13.4*	17.52	15.77*	18.54
8 hours	23.09*	18.42	27.91*	19.77	19.1*	14.96	22.33*	17.45
12 hours	21.26*	21.52	37.48*	27.4	23.8*	20.20	25.99*	22.82
16 hours	23.12*	25.81	46.46*	30.7	26.1*	24.72	29.67*	27.09
20 hours	23.71*	27.71	48.41*	29.98	27.7*	25.96	30.99*	28.18
24 hours	22.85*	27.64	51.67*	29.58	28.7*	26.36	31.90*	28.61

\*P<0.001

## DISCUSSION

Successful treatment of colic is related to its pathophysiology. Both biliary and ureteric colic have obstruction as an essential component, commonly because of calculi and very rarely due to foreign bodies<sup>5</sup>. Obstruction of flow leads to the formation of prostaglandins<sup>6</sup>, which affect local blood flow and sensitise the smooth muscle resulting in a vicious cycle. Fluid dynamics are, to some extent responsible for the genesis of colic.

Much less is known about intestinal colic, though this syndrome has been widely studied in infants. Various factors have been implicated in the genesis of colic, which include oesophagitis and gas formation<sup>9</sup>. Higher urinary levels of 5-hydroxy indole acetic acid have been found in infants with intestinal colic suggesting that serotonin might play an important role<sup>10</sup>. Some dietary factors have also been identified to be responsible for colic in adults, such as mushrooms.

Analgesics have been the mainstay of colic in the past, and dipyron<sup>12</sup>, Kelorolac<sup>13</sup>, piroxicam<sup>1</sup>, diclofenac<sup>14</sup> have all been shown to be effective. Parallel studies, open as well as double blind, have demonstrated the superiority of diclofenac over comparative therapy<sup>15</sup>. Potent inhibition of prostaglandin synthesis by diclofenac is believed to break the vicious cycle of pain, spasm, diuresis<sup>16</sup>. Both the oral and the parenteral form have been studied in renal and biliary colic and found to be highly effective with a large safety margin<sup>17,18,19&20</sup>.

Since there is a difference in the pathophysiology of different types of colic, diclofenac may not produce uniform effect in all types of colic. Use of anticholinergic agents and smooth muscle relaxants like fempiverinium and pitoienone along with diclofenac may provide better control over muscle spasm.

## CONCLUSION

The combination of diclofenac with pitofenone and fempiverinium, in this trial was found to have a good analgesic antispasmodic action that began within 30 minutes following parenteral administration. The effect peaked at 4 to 6 hours, VAS scores suggest that a repeat dose at 8 hours would be more than adequate for patients of biliary colic, some patients may require the repeat dose only after 12 hours. Most patients however, had much lesser pain at even 24 hours post dose than what they had pre-treatment.

There is no significant difference in the effect produced in patients suffering from intestinal, biliary or ureteric colic, in terms of onset of action. After 12 hours post dosing the patients with intestinal, and ureteric colic had a significantly lower pain score than patients with biliary colic. There is also no difference in the side effects produced. Though a rescue medication was provided for, it was used only in twenty-nine patients.

This formulation of diclofenac showed a longer duration of action, than would have been predicted by pharmacokinetics of diclofenac. Against the expected duration of action of 8 to 12 hours, patients of intestinal and ureteric colic experienced relief from pain which lasted as long as 24 hours. Since the study was terminated at 24 hours, it is difficult to comment on further developments. This prolongation of action could be attributed to synergism between antispasmodics and the analgesic properties of the formulation, with a contribution from the reduced prostaglandin levels.

It does appear that smooth muscle spasm has a more important role in colic than was previously believed. Earlier work focussed on the use of analgesics in colic, and analgesics did help. The addition of antispasmodic agents added value to analgesics by prolonging their action, way beyond what was predicted by kinetic studies.

The formulation of diclofenac has demonstrated a wide safety margin. This study suggests that in non-pregnant adults ranging from 16 to 60 years, the formulation may be used safely, following the usual precautions used for agents of this class.

'Manyana™' (combination of diclofenac with pitofenone and fempiverinium) therefore, has rapid onset of analgesic effect (30 minutes), high efficacy and adequate duration of action (ranging from 8-24 hours). The formulation demonstrated adequate safety in the patients evaluated in this clinical trial.

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