

TREATMENT OF BILIARY COLIC WITH PROSTAGLANDIN-SYNTHEASE INHIBITION: DICLOFENAC SODIUM

G N Karachalios
S Tsimiklic
G Asimakis
G Helas

First Department of Medicine
Kalamata General Hospital
Kalamata, Greece

G N Karachalios, MD

S Tsimiklic, MD

G Asimakis, MD

G Helas, MD

SYNOPSIS

Recent reports suggest that the prostaglandin system is involved in the pathogenesis of pain due to biliary colic and drugs inhibiting prostaglandin synthetase have been proposed in the management of this condition. One-hundred and eight patients with biliary colic due to gallstone disease were treated with intramuscular injection of diclofenac sodium (Voltaren) (55 patients) and the anticholinergic Hyoscine-N-Butylbromide (Buscopan) (53 patients) in a double-blind randomized study. Partial or complete relief of pain was achieved within 15 minutes after diclofenac sodium in all patients and in 3 out of 53 receiving Hyoscine-N-Butylbromide ($P < 0.001$). Complete relief of pain was achieved 25 minutes after diclofenac sodium in 44 (80%), compared to none in the Hyoscine-N-Butylbromide group ($p < 0.01$). Four of the patients treated with diclofenac sodium needed a second injection for complete relief of pain during the 24 hours follow-up period. Few side effects were observed.

This study shows that diclofenac sodium administered by the intramuscular route is a very effective drug in treating acute attacks of biliary colic and is an attractive alternative to anticholinergic drugs in the conventional management of this common condition.

INTRODUCTION

Biliary colic is usually treated with intravenous or intramuscular administration of spasmolytic agents. Non-steroidal anti-inflammatory drugs (NSAID's) administered by injection have been proposed as an alternative treatment for biliary colic. (1, 2) Prostaglandin-synthetase inhibition by intramuscular injection of diclofenac sodium, (3) has been shown to relieve biliary colic more effectively than placebo. (4) In this study, partial or complete relief of pain was achieved 15 minutes after the injection in all patients given diclofenac and in two of the 16 given placebo. This beneficial effect may be explained by reduction of the rise in the intraluminal pressure within the gallbladder, mediated by release of prostaglandins in the gallbladder during biliary obstruction. (2) In this study diclofenac sodium, an inhibitor of prostaglandins synthesis, was compared with placebo in a double-blind randomized study in patients with biliary colic.

MATERIAL AND METHODS

Patients with attacks of biliary colic admitted to the emergency department of our hospital were studied. One hundred and eight patients, 53 men and 55 women, aged between 28 to 72 years (mean age 49 years) with gallstone diseases, confirmed by x-ray or at surgery or by ultrasonography, were treated for biliary colic. All patients were examined carefully and blood-pressure, pulse rate and the symptoms were recorded before diclofenac sodium administration and during the observation period at 10, 15, 20, 25, 60, 120, 180 minutes and 24 hours. The patients were randomly allocated to

two treatment groups, corresponding to intramuscular injection of either diclofenac sodium 75 mg and one dose with spasmolytic agent intramuscular Hyoscine-N-Butylbromide (containing 20 mg per Ampoule). Hyoscine-N-Butylbromide was chosen for comparison, since it is one of the preparations most widely used in Greece for treatment of biliary colic. The evaluation of pain intensity was made according to the five point scale (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). All patients had given their informed consent.

Criteria for exclusion were a history of peptic ulcer disease, haemorrhagic disorders, hepatic, renal, cardiac or respiratory failure, diabetes mellitus, known hypersensitivity to NSAIDs and patients who had taken analgesics in the previous two to four hours.

RESULTS

The characteristics of the patients belonging to the different treatment groups are presented in Table 1. Fifty-five patients treated with diclofenac sodium compared with 53 patients treated with Hyoscine-N-Butylbromide. The two groups of patients were similar in sex, age and duration of pain. The medium duration of pain before drug administration was three hours in both groups of patients.

Partial or complete relief of pain was achieved 15 minutes in all patients who received diclofenac sodium and in three of the 53 receiving Hyoscine-N-Butylbromide ($P < 0.001$, χ^2 test). Complete relief of pain was achieved 25 minutes after the diclofenac sodium injection in 44 (80%) of the 55 patients but none in the Hyoscine-N-Butylbromide group (Table II, $P < 0.01$).

TABLE I PATIENTS CHARACTERISTICS ON SEX, AGE AND ASSESSMENT OF PAIN BEFORE TREATMENT WITH DICLOFENAC SODIUM AND HYOSCINE-N-BUTYLBROMIDE

	Diclofenac sodium	Hyoscine-N-Butylbromide
Age	29 — 70	28 — 72
Male	23	24
Female	32	29
Pain		
Moderate	4	4
Severe	38	38
Very severe	13	11

TABLE II RELIEF OF PAIN FROM BILIARY COLIC AFTER TREATMENT WITH DICLOFENAC SODIUM AND HYOSCINE-N-BUTYLBROMIDE

Minutes after injection	Diclofenac sodium group of patients (Number = 55)		Hyoscine-N-Butyl-bromide groups of patients (Number = 53)	
	Partial relief	Complete relief	Partial relief	Complete relief
10	1	0	0	0
15	10	1	1	0
20	15	5	1	0
25	48	44	2	0
30	48	44	0	0
60	48	49	0	0
120		52	0	0
180		55	0	0
24 hours		55	0	0

Pain, estimated by the visual analogue scale (100 mm) was reduced to 62 ± 8 mm (mean \pm SEM) in the patients receiving diclofenac and 6 ± 3 mm in the Hyoscine-N-Butylbromide group ($P < 0.001$). Four patients in the diclofenac sodium group needed another injection of diclofenac sodium for complete relief pain during the 24 hour follow up period. All 53 patients in the Hyoscine-N-Butylbromide group were treated with an injection of 75 mg diclofenac sodium intramuscularly after 25 minutes due to persistent pain. Thirty-two of the 53 patients (60.2%) achieved partial relief of pain and 28 complete relief of pain after 30 minutes.

No significant side-effects were observed within the observation period. Nausea was recorded in 4 patients receiving diclofenac sodium. Headache and dizziness were registered in 2 patients receiving diclofenac sodium and in 1 patient receiving Hyoscine-N-Butylbromide. No statistically significant changes in blood pressure and pulse rate in the two groups of patients were observed.

DISCUSSION

This double-blind randomized study shows that intramuscular injection of diclofenac sodium, a compound that inhibits prostaglandin synthesis, is very effective in treating patients with attacks of biliary colic. The beneficial effect of diclofenac sodium in patients with biliary colic due to gallstone disease indirectly suggests that prostaglandins play an important role in the pathogenesis of pain due to biliary colic. The rationale for using a NSAID in the treatment of biliary colic is based on the findings that there is an increased synthesis and release of prostaglandins, which are of important pathogenetic value in this condition. (2, 4, 5) Similar results with intramuscular administration of diclofenac sodium have been reported by Broggin et al (3) in 14 patients with biliary colic. Thornel et al (1) reported similar results with intravenous injection of indomethacin in 20 patients treated for 24 attacks of pain associated with gallstone, but undesirable side-effects presented in 60% of the case. Since diclofenac is more potent than indomethacin, intramuscular administra-

tion was used in this study to simplify administration and this route may have accounted for the lack of side-effects in our study. Probably the intravenous administration has a faster effect in patients with severe pain but our results compared to indomethacin are not very different as to the time of action.

Our clinical results with diclofenac sodium were significantly more effective in the treatment of biliary colic than with a commonly-used anticholinergic drug. Because opiate drugs are contraindicated in the treatment of biliary colic, potent inhibitors of prostaglandin-synthetase, such as diclofenac sodium, may offer a good alternative in this condition. The side-effects of this drug were less common than with other drugs in the short-term.

In conclusion, our findings show that 75 mg diclofenac sodium given intramuscularly is an effective treatment for attacks of biliary colic and we suggest that this treatment is an attractive alternative that might replace anticholinergic drugs in the conventional management of this very common and painful condition.

REFERENCES

1. Thornell E, Jansson R, Kral JG, Svanvik J: Inhibition of prostaglandin synthesis as a treatment of biliary pain. *Lancet* 1979; 1: 584.
2. Sacchetti G, Caputo G, Mandeli V, Forari R, Magani E: Biliary colic as a model for assessing analgesic activity in man. *J Pharmacol Exp Ther* 1977; 201: 444-9.
3. Broggin M, Corbetta E, Grossi E, Borghi C: Diclofenac sodium in biliary colic: a double-blind trial. *Br Med J* 1984; 288: 1042.
4. Morton IKM, Saverymuttu SH, Wood JH, Wood JR: Inhibition by prostaglandins of fluid transport in the isolated gall-bladder of the guinea pig. *Br J Pharmacol* 1974; 50: 460 p.
5. Heintz CK, Leinesser W, Peterson KU, Heindenreich O: Triphasic effect of prostaglandins E1, E2, and F1 alpha on the fluid transport of isolated gall-bladder of guinea pigs. *Prostaglandins* 1975; 9: 309-92.