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Original Research Article

A prospective, multicentric study to determine the safety and effectiveness of fixed-dose combination of camylofin dihydrochloride and nimesulide in patients presenting with acute colicky abdominal pain in India

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ABSTRACT

Background: Spasmolytics and NSAIDs are a therapy of choice in colic pain. However, the tolerability and effectiveness of this combination remains unexplored. The aim of this prospective, single-arm, open label, multicenter study was to evaluate the safety and effectiveness of Anafortan-N® (fixed-dose combination of camylofin dihydrochloride 50 mg + nimesulide 100 mg) in patients with acute colicky abdominal pain.
Methods: In all, 295 patients with acute colicky abdominal pain and at least one episode of colicky pain in the last 24 hours were enrolled in this study. None of the patients were hospitalized. All patients were advised Anafortan-N® tablets twice daily orally for 5 days. The safety of Anafortan-N® was assessed by number and percentage of patients with adverse events (AEs) and change in the severity and frequency of AEs by the end of treatment. The tolerability was determined by number and percentage of patients who had to discontinue the treatment due to AEs. The effectiveness was evaluated as percentage change in the mean intensity of pain score (based on a 100-mm visual analog scale) from baseline to end of treatment.
Results: Overall, 14 (4.7%) patients reported 14 AEs, all of which were treatment-emergent and non-serious. Of the 14 AEs, 7 AEs were mild, 6 AEs were moderate, and 1 AE was severe. No serious adverse events (SAEs) were reported. No adjustment of the study medication was required in response to any of the AEs, and none of the AEs led to discontinuation of the study treatment. At end of treatment (EOT), the pain intensity significantly ($p<0.0001$) reduced to 1.7±5.49 with a mean change of -69.9±17.42 from baseline, and the daily pain intensity significantly ($p<0.0001$) reduced to 0.1±0.38 with a mean change of -3.5±1.77 from baseline.
Conclusions: Among Indian patients presenting with acute abdominal colicky pain, twice daily treatment with a FDC of camylofin dihydrochloride 50 mg and nimesulide 100 mg (Anafortan-N®) showed significant reduction in pain intensity with very few side effects, thereby confirming its safety, tolerability, and effectiveness in acute colicky abdominal pain.

Keywords: Camylofin, Colicky pain, Nonsteroidal anti-inflammatory drugs, Spasmolytic, Nimesulide

INTRODUCTION

Abdominal pain is a common condition requiring medical attention.[1] Acute colicky abdominal pain is typically a sharp, localized urinary or gastrointestinal pain and is usually abrupt and spasm-like. This pain can arise repeatedly over weeks or even months. Typically, three types of colic pain are seen in adults: biliary colic pain (usually caused by gallstones), renal colic pain (often related with urinary or kidney stones), and intestinal colic pain (caused by blockage of small or large intestines that prevents passing of liquid and food through the body).[1] The major factors responsible for pain in visceral organs are abnormal contraction and distension of the hollow structures, traction or compression of ligaments, stretching of the capsule of solid visceral organs, ischemia of visceral musculature, and accommodation of algogenic substances.[2] In addition, pain could result from muscle contraction around partial or complete blockage in any of the hollow organs.

Lifetime prevalence of colicky abdominal pain in adults is approximately 25%.[3] The global incidence of abdominal pain ranges from 16% to 22% in subjects aged >65 years.[4] Colic pain is also witnessed in 10% to 25% of infants with approximately 90% of cases occurring in the first few months of life.[5,6] An annual worldwide incidence of renal colicky pain has been found to be approximately 16/10,000 people, and a lifetime incidence of 2% to 5% with a reoccurrence rate of ~50% has been reported.[7]

Analgesic, spasmolytic, and anticholinergic agents play supportive roles in reducing symptoms and enhancing quality of life of patients with acute colicky abdominal pain. The dose and duration of treatment with these agents should be modified based on symptoms and use of supplementary anti-inflammatory drugs.[8]

In recent years, fixed dose combination (FDC) drugs have emerged as a treatment of choice owing to proven advantages like synergistic effects, low risk of drug resistance, good tolerability, complementary mechanisms of action, and cost effectiveness. Moreover, administering FDCs is a rational approach to achieving optimal therapeutic benefits while limiting pill burden. Use of spasmolytic-analgesic combination to treat abdominal pain has shown substantial reduction in abdominal pain intensity relative to placebo.[9,10] Anafortan-N® is an FDC of camylofin dihydrochloride 50 mg and nimesulide 100 mg) that is expected to be a promising therapy for acute colicky abdominal pain.

One of the two drugs in this FDC is camylofin dihydrochloride, which mainly acts on smooth muscles of the cervix, intestine, and ureter, whereas its impact on eyes, glands, circulation, and heart is minimal and without clinical significance. The efficacy and safety of camylofin dihydrochloride as a spasmolytic agent has been demonstrated in several clinical studies.[11-14] Since more than five decades, camylofin dihydrochloride, a potent and safe antispasmodic, in a dose of 25 mg administered intravenously or intramuscularly, has been used to treat symptoms related to biliary, renal, and ureteric colic pain, and menstrual pain.[2] A study conducted in the Indian population showed a substantial increase in antispasmodic effect of camylofin dihydrochloride when used intravenously along with nonsteroidal anti-inflammatory drugs (NSAIDs).[15]

The other therapeutic agent in the FDC is nimesulide, which is an NSAID with relatively selective inhibitory potential toward cyclooxygenase-2 (COX-2) and possesses analgesic and antipyretic properties. Nimesulide has been found to exert therapeutic effects by targeting not only COX-2 mediated prostaglandins, but several other key modulators of the inflammatory process, such as proteolytic enzymes, free radicals, and histamine. Nimesulide is a therapy of choice for acute painful situations wherein acute inflammation is the predominant component. Nevertheless, limited literature is available on the safety and effectiveness of the FDC of camylofin dihydrochloride and nimesulide for the treatment of colicky pain in the Indian population.

The objective of the present study was to assess the safety, tolerability, and effectiveness of this FDC in Indian patients with acute colicky abdominal pain.

METHODS

Study design

This prospective, single-arm, open-label, study was conducted between November 2018 and July 2019 across 5 centers in India in compliance with good clinical practices (GCP) guidelines and applicable national regulations [Indian regulatory guidelines (Indian council of medical research [ICMR] and Indian GCP guidelines]. Written informed consent was obtained from all patients before enrollment. Patients were assigned a unique identification number to maintain confidentiality, and this number was not reassigned to any other patient in any case. The study involved a total of 3 site visits: 1 baseline visit on day 1, 1 follow-up visit on day 3 (±1 day), and 1 follow-up visit on day 6 (±1 day) or at end of treatment (EOT). Patients were instructed by the investigator to take Anafortan-N® tablets twice daily orally for 5 days. The post therapy follow-up was done for patients with ongoing adverse events (AE) or serious AEs (SAEs). In patients experienced AEs during the treatment period, they were asked to report to the study site for further evaluation and investigations by the study physician.

Eligibility criteria

Male or female subjects aged 18-65 years with acute colicky abdominal pain and a history of at least one episode of colicky pain within 24-hours prior to screening, with no other concomitant illness, were enrolled. Patients who had been taking Anafortan-N® or any other

prescription analgesics, or antispasmodic medications within the previous week before study enrollment were excluded. Exclusion was also based on history of hypersensitivity/allergy to study drug, cognitive impairment, alcohol abuse, psychiatric illness that would affect the ability of the patient to complete patient diary and other assessments, or any other illness or conditions that in the opinion of the investigator did not justify inclusion of a patient in the study. Pregnant or lactating women were also excluded.

Study endpoints

The primary endpoints of the study included evaluation of the number and percentage of patients with AEs including abnormal levels of laboratory (serum chemistry and hematological) parameters, including severity of the AEs (per common terminology criteria for adverse events [CTCAE] criteria), and drug-event relationship on day 6/ EOT visit or up to AE follow up post treatment as applicable. Change in the severity and frequency of AEs including significant changes in laboratory parameters from baseline to day 3, day 6, and up to AE follow up post treatment (as applicable) were also assessed.

Secondary endpoints included assessment of the effect of Anafortan-N® tablets on pain intensity as measured by change in the mean intensity of pain (based on the 100-mm visual analog scale [VAS]) from baseline to EOT, change in frequency of daily pain episodes from baseline to EOT, ≥30-mm reduction in pain score from baseline to EOT, and physician's global assessment (PGA) of effectiveness and tolerability at EOT on a scale of 1 (no change) to 7 (great deal better). Tolerability was assessed as the number and percentage of patients who had to discontinue treatment due to AEs before study completion.

Statistical analysis

The sample size was calculated based on gastrointestinal (GI)-related AE rates reported in the literature for nimesulide and assuming that camylofin dihydrochloride had a similar safety profile. A sample size of 294 patients was estimated considering an incidence rate of GI-related AEs of 6.6% with a 3% margin at 95% confidence level and a 10% drop out rate. All the study participants constituted the analysis population. The study endpoints were analyzed using descriptive statistics. Continuous variables were presented as mean (standard deviation [SD]) and categorical variables as frequency and number of patients. Statistical tests were performed at 5% level of significance. AEs were coded using medical dictionary for regulatory activities version 22.1.

RESULTS

Demographics and baseline characteristics

A total of 295 patients were screened and enrolled in the study, of which 291 (98.6%) patients completed the study. Three patients withdrew consent and 1 patient was lost to follow up. Approximately 60% of the study cohort consisted of male patients (Table 1). Mean (SD) age of the study cohort was 36.7 (11.62) years. All enrolled patients had a history of intermittent colicky pain with a mean of 3.6 (1.72) pain episodes per day for approximately 30 minutes. At the baseline visit, 98 (33.2%) patients experienced vomiting, and 70 (23.7%) had nausea associated with abdominal pain. The frequency of these symptoms was intermittent in majority of patients (228 [77.3%]) with the mean (SD) of the 2.64 (1.12) pain episodes.

Table 1: Demographics and the baselines characteristics.

Parameters	Overall, (n=295)
Age in years, mean (SD)	36.7 (11.62)
Male gender, n (%)	175 (59.3)
Asian race, n (%)	295 (100.0)
BMI (kg/m^2), mean (SD)	24.0 (3.16)
History of colicky abdominal pain, n (%)	
Intermittent frequency	295 (100.0)
Number of pain episodes per day, mean (SD)	3.6 (1.72)
Location, n (%)	
Right upper quadrant	48 (16.3)
Right lower quadrant	46 (15.6)
Left upper quadrant	37 (12.5)
Left lower quadrant	40 (13.6)
Suprapubic	13 (4.4)
Epigastric	105 (35.6)
Periumbilical	27 (9.2)
Other	2 (0.7)
Duration of pain episodes in minutes, mean (SD)	29.9 (20.20)

Safety evaluation

As high as 98% of patients (289/295) were compliant to the study drug. As depicted in

Table 2, 14 (4.7%) patients reported 14 AEs, all of which were treatment-emergent and of non-serious type (AE, adverse event; CTCAE, common terminology criteria for adverse events criteria.). Of the 14 AEs, 7 were mild, 6 were moderate and, 1 AE was severe. Of the total 14 AEs, 6 AEs were related to infections and infestations (bacterial or fungal urinary tract infection and gastroenteritis) were reported. Two AEs of increased blood bilirubin and one AE of increased transaminase was reported. Two AEs related to renal and urinary disorders (crystalluria and nephrolithiasis) and 1 AE each of gastrointestinal disorders (mouth ulceration), skin and subcutaneous tissue disorders (pruritis) and metabolism and nutrition disorders (decreased appetite) were reported. No clinically significant abnormality was reported in renal function. All

the treatment-emergent AEs (TEAEs) were mild in intensity, except for 6 TEAEs of moderate intensity (2 AEs of bacterial urinary tract infection, 2 AEs of gastroenteritis, and 1 TEAE each of increased blood bilirubin or increased transaminase). One (7%) patient reported increased blood bilirubin of severe intensity. All TEAEs were found to be unrelated to the study drug, except 1 for TEAE of pruritis a patient that was thought to be related to the study drug. All TEAEs resolved, except for 1 TEAE of fungal urinary tract infection in a patient for whom the outcome was unknown. No adjustment of the study medication was required in response to any of the AEs, and none of the AEs required treatment discontinuation.

Table 2: Summary of adverse events.

Variables	Parameters	Number of events	Number of patients	Percentages of patients (%)
Total events	-	14	14	4.7
Severity CTCAE	Mild	7	7	2.4
	Moderate	6	6	2.0
	Severe	1	1	0.3
Serious AE	Yes	0	0	0.0
	No	14	14	4.7
Drug-event relationship	Unrelated	13	13	4.4
	Possible	1	1	0.3
Action taken with study drug	None	14	14	4.7
Outcome four categories	Resolved	13	13	4.4
	Unknown	1	1	0.3
Led to study termination	No	14	14	4.7

AE, adverse event; CTCAE, common terminology criteria for adverse events criteria.

Table 3: Summary of treatment emergent adverse events by severity and drug -event relationship.

Adverse event	Events (% of patients), n (%)	Severity	Drug-event relationship	Outcome
Mouth ulceration	1 (0.3)	Mild	Unrelated	Resolved
Gastroenteritis	2 (0.7)	Moderate	Unrelated	Resolved
Urinary tract infection bacterial	3 (1.0)	Mild (n=1), Moderate (n=2)	Unrelated	Resolved
Urinary tract infection fungal	1 (0.3)	Mild	Unrelated	Unknown
Blood bilirubin increased	2 (0.7)	Moderate (n=1), Severe (n=1)	Unrelated	Resolved
Transaminases increased	1 (0.3)	Moderate	Unrelated	Resolved
Decreased appetite	1 (0.3)	Mild	Unrelated	Resolved
Crystalluria	1 (0.3)	Mild	Unrelated	Resolved
Nephrolithiasis	1 (0.3)	Mild	Unrelated	Resolved
Pruritus	1 (0.3)	Mild	Possible	Resolved

Table 4: Summary of change in intensity and frequency of pain in the study subjects.

Parameter, mean (SD)	Baseline (Visit 1)	EOT	Change from baseline	95% CI	P value
Intensity					
All patients*	N=295	N=295	N=295		
VAS score	71.6 (15.66)	1.7 (5.49)	-69.9 (17.42)	-71.88, -67.89	<0.0001
Patients with meaningful pain relief†	N=289	N=289	N=289		
VAS score	72.3 (14.87)	1.3 (4.31)	-71.0 (15.66)	-72.83, -69.21	<0.0001
Frequency*	N=295	N=295	N=295		
Daily pain episodes	3.6 (1.72)	0.1 (0.38)	-3.5 (1.77)	-3.68, -3.28	<0.0001

P values were calculated using paired t-test for comparison of change from baseline. *For 283 subjects, EOT was on day 5; for the remaining 12 subjects, EOT was from day 3 to day 10. † For 279 subjects, EOT was on day 6; for the remaining 10 subjects, EOT was from day 3 to day 10. EOT, end of treatment; SD, standard deviation; VAS, visual analog scale.

Effectiveness evaluation

Pain intensity as assessed by VAS was significantly ($p<0.0001$) reduced to 1.7 (5.49) with a mean change of -69.9 (17.42) from baseline, and daily pain intensity was significantly ($p<0.0001$) reduced to 0.1 (0.38) with a mean change of -3.5 (1.77) from baseline value of 71.6 mm (Table 4). A total of 289 subjects had absolute (≥30-mm change) and meaningful relief in pain with a mean change of -71.0 (15.66) in pain intensity from baseline. Based on PGA scores, majority of the subjects had considerable (130 [44.1%]) or definite (121 [41.0%]) reduction in pain intensity as shown in Table 5.

Table 5: Summary of physician's global assessment of effectiveness and tolerability at visit 3 (Day 6).

Category, n (%)	Visit 3 (n=295)*
PGA score	
No change (or condition has got worse)	0 (0.0)
Almost the same, hardly any change at all	1 (0.3)
A little better, but no noticeable change	0 (0.0)
Somewhat better, but the change has not made any real difference	0 (0.0)
Moderately better and a slight but noticeable change	39 (13.2)
Better and a definite improvement that has made a real and worthwhile difference	121 (41.0)
Great deal better and a considerable improvement that has made all the difference	130 (44.1)

*Out of 295 subjects, 4 subjects did not complete the study: 1 patient was lost to follow up and 3 withdrew consent. PGA, physician's global assessment.

DISCUSSION

Combination therapies are expected to provide greater effectiveness and reduced risk of adverse reactions at lower costs with improved medication concordance compared with high-dose monotherapies.[16] In colicky abdominal pain, the combination of antispasmodic and analgesic agents has become the treatment of choice. Anafortan-N® is an FDC of camylofin dihydrochloride 50 mg (anti-spasmodic) and nimesulide 100 mg (analgesic) that is being increasingly used in clinical practice for its synergistic effect in providing pain relief. In this study evaluating the safety and effectiveness of Anafortan-N® tablets in Indian patients with acute colicky abdominal pain in the real-world setting, a good safety and tolerability profile of Anafortan-N® tablets given for 5 days (twice daily) was observed with only ~5% of the study cohort reporting 14 TEAEs.

All the events were non-serious and majority of them were unrelated to the study drug. The adverse events included urinary tract infection (bacterial and fungal), gastroenteritis, mouth ulceration, increased transaminase and blood bilirubin levels, decreased appetite, crystalluria, nephrolithiasis and pruritis. Published literature suggests allergic skin reactions, headache, dizziness, vomiting, gastric/mouth ulcers as the common side effects of camylofin.[2] Gastrointestinal disorders and increased hepatic enzymes are the most common side effects of nimesulide, renal and urinary, cardiac, and immune system disorders have been rarely observed.[17] The adverse effects recorded in our study were comparable to the known side effects of both the drugs. All AEs was resolved, except for 1 AE of fungal urinary tract infection for which the outcome was unknown. Moreover, no adjustment of study medication was required in response to any of the AEs, and none of the AE led to treatment discontinuation.

With regard to effectiveness, the study recorded a decrease in pain intensity on the 100-mm VAS scale post administration of the FDC. A significant reduction ($p<0.0001$) in pain intensity was recorded after 5 days of treatment. Consequently ~95% of the study cohort achieved a meaningful change in pain, i.e., 30-mm decrease in pain from baseline. While most of the published literature has provided evidence on effectiveness of camylofin in obstetrics, very few studies have reported its effectiveness in abdominal colic pain.[14,18-21] An Indian study on patients with intestinal, renal and biliary colic pain demonstrated effective pain relief in more than 94% of study patients when treated with 25 mg camylofin.[14]

In our study, the effectiveness of the FDC in reducing pain was further corroborated using the PGA tool wherein approximately 44% of the patients demonstrated considerable reduction in the pain intensity and majority (approximately 85%) of the cohort felt better after 5 days of treatment.

This is the first of its kind pan India study to demonstrate real-world evidence for safety and effectiveness of the FDC in patients with acute colicky abdominal pain. Moreover, the PGA and VAS questionnaires used in the study were administered to the patients by an investigator or a designee, which enabled to capture information with greater accuracy and confidentiality.

The main limitation of this study was its relatively short treatment duration because of which long-term safety outcomes could not be determined. Furthermore, being an observational study, no comparator analysis was performed. Also, as the pain severity is highly subjective and variable from patient to patient, using pain scores alone may not be adequate to support the observed evidence.

CONCLUSION

This study conducted among Indian patients diagnosed with acute colicky abdominal pain showed that twice daily treatment with fixed dose combination of camylofin dihydrochloride 50 mg and nimesulide 100 mg had a good safety and tolerability profile with very few treatment-emergent AEs and highly significant reduction in pain intensity from baseline to end of treatment.

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