Adjunctive treatment of decompression illness with a non-steroidal anti-inflammatory drug (Tenoxicam) reduces compression requirement.

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Bennett M, Mitchell S, Dominguez A. Adjunctive treatment of decompression illness with a non-steroidal anti-inflammatory drug (Tenoxicam) reduces compression requirement. Undersea Hyperb Med 2003; 30(3):195-205 - We report a randomized trial examining adjunctive administration of the NSAID, tenoxicam, to divers suffering with DCI. 180 subjects were graded for severity on admission and randomized according to a stratified random number schedule. Subjects were recompressed and treatment continued daily until symptom stabilization or complete resolution. Tenoxicam 20mg or a placebo preparation was administered at the first air break during the initial recompression and continued daily for seven days. The subjects were assessed using a recovery status score at the completion of treatment and at 4-6 weeks. The proportion of patients with mild residual symptoms at discharge and final follow-up was not significantly different (discharge placebo 30% versus tenoxicam 37%, *P*=0.41; six weeks placebo 20% versus tenoxicam 17%, *P*=0.58). There was a significant reduction in the number of treatments required to achieve discharge (median treatments placebo 3, tenoxicam 2, *P*=0.01). 61% of patients in the tenoxicam group required less than 3 compressions, versus 40% in the placebo group (P=0.01, RRR 33% [95%CI 9%-56%], NNT=5 [95%CI 3-18]). There was no evidence of increased complications of treatment in the tenoxicam group. When given this NSAID, patients with DCI require fewer hyperbaric oxygen (HBO_2) sessions to achieve a standard clinical end-point and there is likely to be an associated cost saving.

Decompression illness, non-steroidal, Tenoxicam

INTRODUCTION

Decompression illness (DCI) is a disease of compressed gas divers, aviators, and astronauts caused by formation of intracorporeal bubbles (1). A reduction in environmental pressure ("decompression") may provoke bubble formation by two mechanisms. First, there is a proportional reduction in the solubility of inert gas dissolved in venous blood or the tissues, and this gas may form bubbles. Second, if air is trapped in the lungs at pressure, expansion during decompression may damage the lung tissue and result in introduction of bubbles to the pulmonary veins. The resulting vascular and tissue bubbles may provoke symptoms by direct mechanical effects (2), interruption of tissue perfusion (3), and/or by activation of leukocytes (4) as well as a variety of secondary processes such as the clotting (5), complement (6), and kinin (7) cascades. There is a broad spectrum of potential symptoms and severity in clinical DCI, but most cases suffer a mild form characterized by musculoskeletal pain, parasthesias and vague constitutional symptoms such as fatigue and malaise (8).

Definitive treatment of DCI involves recompression and administration of HBO_2. Although there are variations, a typical regimen for treatment of air divers involves an initial recompression according to the protocol specified by US Navy Treatment Table 6 (USN TT6), followed by shorter, once or twice daily follow-up recompressions (9). Despite the use of such widely accepted algorithms, complete recovery is not invariable (8, 10, 11), and decisions about when to stop recompression treatment in incompletely recovered patients can be difficult. A common approach is to continue with daily follow-up recompressions until symptoms have either resolved or there is no further sustained improvement following each treatment (12). However, degrees of improvement are often difficult to judge, especially where symptoms are mild, fluctuating, and subjective. Moreover, although the natural history of mild symptoms such as musculoskeletal pain is for eventual spontaneous recovery (13), refractory cases are sometimes seen. It follows that decisions to continue or withdraw recompression treatment may be complicated by uncertainty over both the progress and significance of the symptoms.

Pharmacological adjuvants to recompression, such as corticosteroids (14), aspirin (15), heparin (16) and lidocaine (17) have been proposed. At the present time only lidocaine is strongly supported, and only for the treatment of cerebral arterial gas embolism (18). In every case, these agents have been targeted primarily at pathophysiological processes that contribute to the more serious symptoms of DCI. Little attention has been directed at agents that might hasten resolution of mild symptoms such as musculoskeletal pain and fatigue.

Douglas (1986) suggested the use of non-steroidal anti-inflammatory drugs (NSAIDs) for relief of musculoskeletal pain in DCI (19), and many diving physicians are known to use them empirically in this context. In the only formal investigation of NSAIDs in DCI, indomethacin exhibited some protection of neuroelectrical function in dogs subjected to cerebral arterial gas embolism, but only when administered with heparin and prostaglandin I_2 (20). Despite this paucity of relevant data, the administration of NSAIDs makes biological sense. For example, although the exact mechanism of musculoskeletal pain in DCI is unknown, one possibility is that it is due to bubble formation in periarticular soft tissues such as tendons (21), ligaments, or even the joint capsule itself (22). The pain might arise from a direct effect of bubbles on pain sensitive structures (23) or from inflammatory processes such as activation of the arachidonic acid cascade by bubble-induced tissue damage. Conversion of arachidonic acid to the various prostaglandins by cyclo-oxygenase (COX) potentiates the hyperalgesic effect of bradykinin by sensitizing afferent C fibres (24). Prostaglandins are also implicated in causation of the fever and constitutional symptoms of infection, and the secondary phase of platelet aggregation (25). It is possible they play a similar role in DCI. Once initiated, the latter processes might be unaffected by subsequent resolution of bubbles, and this might explain the troublesome persistence of low-grade pain and constitutional symptoms despite recompression.

The NSAIDs block conversion of arachidonic acid by inhibiting COX (24), and thereby help settle these inflammatory processes. It follows that administration of NSAIDs in conjunction with recompression and HBO_2 might promote more rapid and clearly defined resolution of mild DCI symptoms, thus facilitating earlier termination of recompression therapy. The extent to which prostaglandin-mediated inflammation contributes to the refractory symptoms in some patients is unknown, but it is plausible that therapy with NSAIDs might result in a greater proportion of complete recoveries, especially in the short term. A trial in humans is the only investigation likely to demonstrate any such effect on relatively subjective and subtle manifestations, since these would be difficult to replicate and monitor in animal models. Furthermore, as these agents are already in use, such a trial is necessary to assess clinical practice

alternatives. This randomized double-blind study investigates the hypotheses that administration of NSAIDs in conjunction with recompression and HBO_2 may both increase the proportion of patients achieving complete recovery in the short term and reduce the number of treatments required to achieve resolution or plateau of symptoms in DCI.

MATERIALS AND METHODS

After obtaining institutional ethics committee approval and written informed consent, 180 recreational divers with a clinical diagnosis of DCI were enrolled from three separate institutions (The Prince of Wales Hospital Sydney, HMAS Penguin School of Underwater Medicine Sydney and The Wesley Hospital Brisbane). Subjects were eligible for inclusion when a diagnosis of DCI was made, along with a decision to recompress. Patients were excluded if a cerebral arterial embolism was suspected clinically, or they had received a non-steroidal analgesic prior to arrival at the hyperbaric facility, regularly took such medication, or had a history of asthma or sensitivity to NSAIDs. Recruitment began in November 1997 and continued to March 2002, during which time a total of 197 eligible patients were treated in the three facilities (10% loss of recruitment).

On entry into the study, subjects were graded 1 – 5 according to severity after Bond et al (Table 1) (26). Subjects were allocated to receive either an active preparation of Tenoxicam (Roche Pharmaceuticals, Sydney) 20mg daily, or a placebo preparation identically presented and supplied by the drug manufacturer. Allocation was achieved using a computer generated, randomized schedule, stratified by admission grade. Only the trial pharmacist knew the schedule, while the investigators, subjects, treating physicians and outcome assessors were all unaware of group allocation.

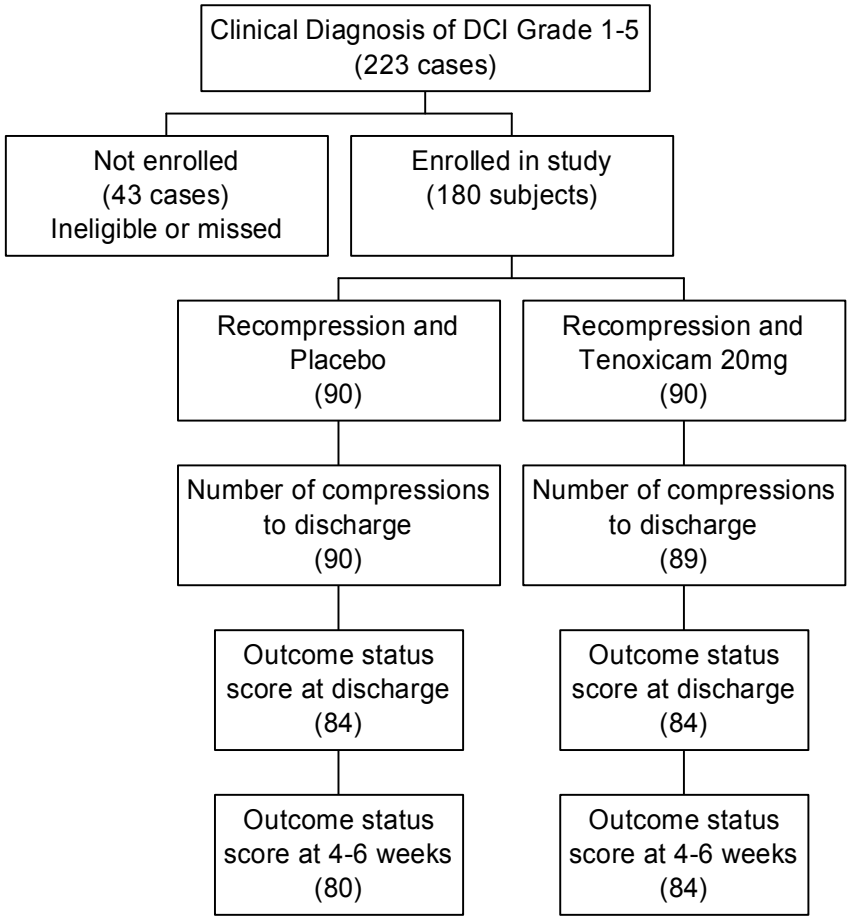
Table 1. Presentation Severity Grade at Admission (from 26).

Presentation severity grade	Description of symptoms and signs
One	Musculoskeletal pain, rash, itching
Two	Musculoskeletal pain and / or mild neurological symptoms such as paraesthesiae, headache, mild fatigue and restlessness.
Three	Severe pain and / or neurological symptoms and signs such as tinnitus, vomiting, severe fatigue and reflex changes
Four	Clear neurological symptoms with objective signs such as numbness, weakness, dyscoordination, and cognitive dysfunction
Five	Severe neurological dysfunction such as marked weakness / paralysis, speech or visual disturbance, bladder or bowel dysfunction
Six (excluded)	Rapid onset, severe neurological manifestations such as semi- or unconsciousness, and convulsions with suggestive profile for CAGE

The trial procedure is summarized in Figure 1. Patients presenting to the recompression facility with a possible diagnosis of DCI were interviewed and examined by an experienced diving physician. They were considered for entry into the trial if the examining physician made a

clinical diagnosis of DCI at that time. Recompression therapy was instituted on a schedule chosen by the treating hyperbaric physician, usually a USN TT6 followed by 2.4 ATA 90 minute oxygen tables as required, although there were some variations. In 3 subjects, the initial compression was a 2.4 ATA 90 minute oxygen table while 9 subjects had 1.9 ATA 120 minute oxygen tables for follow-up treatments (see Table 4).

Figure 1. Conduct of Trial and Losses to Follow-up



At the first air break, the subjects were reassessed in order to determine the early effectiveness of oxygen recompression at 2.8ATA (18msw), and the initial dose of trial medication was administered. The subsequent treatment course was conducted at the treating physician's clinical discretion with the general operating rule of continued daily oxygen treatments at 2.4ATA for 90 minutes until complete resolution of symptoms plus one further treatment, or a plateau in improvement over two consecutive daily treatments. Trial medication was continued daily from the morning following the first treatment to a total of 7 doses and then ceased. Drug ingestion was witnessed during the days of recompression, while subsequent compliance was assessed by self-reporting. The number and profile of all treatments was recorded along with demographic information, diving details, method of retrieval and time from first symptoms to recompression. Subjects were clinically assessed by the treating physician at

discharge, and a follow-up visit at 4-6 weeks. A clinical outcome scoring system was applied (Table 2) and used for statistical comparison.

Table 2. Outcome score recorded at discharge and follow-up visit (4-6 weeks).

Outcome Score
1. Well, no symptoms or signs
2. Minor symptoms or signs not effecting daily life (Examples: Intermittent tingling in an extremity or minor discomfort not requiring analgesia)
3. Moderate symptoms or signs resulting in some effect on daily life (Examples: Continued pain requiring analgesia, weakness, hypoasthesia)
4. Major symptoms or signs significantly effecting life (Examples: Paraparesis, cognitive dysfunction requiring employment change)
5. Dead

Statistical power and analysis:

Previous analysis of outcomes at Prince of Wales Hospital (10), suggested that we could expect approximately 30% of those treated for DCI to be discharged with some residual symptoms (outcome score >1). We considered a clinically significant benefit from NSAID treatment in this study would be demonstrated by a reduction in this rate to 20%. Our power calculation suggested we would need a sample size of approximately 180 subjects in order to have an 80% chance of detecting such a difference at a significance level of 0.05.

All analyses were performed using StatsDirect software, version 1.9.8 (Iain E. Buchan, 2001). Data were analyzed using chi-square statistics for difference in proportions, (normal approximation method for larger samples, Fisher's Exact for smaller), Wilcoxon Rank Sum Test for the comparison of non-parametric data and Student *t*-test for comparison of parametric data. Differences detected were considered to be statistically significant at a two-sided *P*-value of less than 0.05. All analyses were made on an intention to treat basis.

RESULTS

180 subjects were enrolled in the study during the data collection phase. During this time 43 cases were not enrolled (19% loss to enrollment), of which 6 refused consent, 12 had a medical contra-indication to NSAID administration, 8 had already taken analgesia and 17 were eligible but missed recruitment (10% failure to recruit). The majority of cases were mild neurological (Grade 2) symptoms (Table 3).

Demographic data and the distribution of other potential confounders are summarized in Table 4. There was no apparent uneven distribution of any of these attributes, and no further statistical manipulation of the data was made with respect to confounding variables.

Table 3. Severity Grades at Presentation.

Presentation Grade	Number (%) of cases Placebo/tenoxicam
Grade 1	15 (8.3) / 19 (10.6)
Grade 2	57 (31.7) / 56 (31.1)
Grade 3	6 (3.3) / 5 (2.8)
Grade 4	6 (3.3) / 6 (3.3)
Grade 5	6 (3.3) / 4 (2.2)

90 subjects were assigned to receive tenoxicam and 90 to receive placebo. One patient in the tenoxicam group had a lost record and does not contribute data at any point. In addition, 11 further patients did not have a discharge health score recorded and 4 further patients did not return for follow-up at 4 to 6 weeks following discharge (Figure 1), giving a loss at final follow-up of 16 patients (8.9%). 179 subjects contributed data to the number of treatments required prior to discharge.

Table 4. Demographics and Possible Confounders.

Characteristic	Placebo Group (n=90)	Tenoxicam Group (n=89)
Age (yrs)	30.8	31.5
Male	66 (73%)	68 (76%)
Onset time to recompression (hrs)	24 (median)	24 (median)
Altitude >500m during retrieval	17 (19%)	15 (16%)
Violated table or computer*	44 (49%)	45 (51%)
Initial treatment table used:		
USN TT6/USN TT5/Other±	78(87%)/9(10%)/3(3%)	81(91%)/8(9%)/0
Reported missing >50% of tablets	4 (4%)	4 (4%)
Revised diagnosis on discharge	7 (8%)	9 (10%)
Problems during compression	3 (3%)	3 (3%)

*Physician noted clear violation of table or computer algorithm in use.
±Includes Royal Australian Navy treatment table – 1.9ATA for 90 minutes breathing oxygen with two 5-minute air breathing periods followed by a 30 minute decompression to the surface on 100% oxygen and the POWH 2.4ATA, 90 minute oxygen table.

Eight subjects admitted to ceasing their medication before the course was half completed. Of the four in the tenoxicam group, two complained of nausea and two felt they had 'the flu'. Of the four in the placebo group, one complained of nausea, two did not state a clear reason and one had a diagnosis made of inner ear barotrauma (IEBT) following the first compression (medication ceased by the treating physician).

Six subjects had problems during initial recompression. Three subjects (one active, two placebo) complained of aural barotrauma, two (one active, one placebo) developed premonitory signs of cerebral oxygen toxicity and one tenoxicam patient complained of nausea not resolved by removal from oxygen breathing at depth.

Sixteen subjects (9%) had a revised diagnosis by the time of discharge. Six were felt to have a musculo-skeletal injury responsible for their symptoms, three developed a respiratory tract infection, two were reclassified as IEBT, and one as likely to be a cerebral arterial gas embolism. In the remaining four subjects the diagnosis was changed to salt water aspiration, hysterical paralysis with pseudoseizures, Hepatitis B and 'unknown' respectively.

The major outcomes are summarized in Table 5. There was no significant difference between the groups in terms of health status score at discharge or subsequent review at between 4 and 6 weeks. The proportion of subjects with an outcome score at discharge of >1 was 30% in the placebo group and 37% in the tenoxicam group, (7% difference in favor of placebo, $P = 0.41$, 95% CI 21% to –7%). At the second review the figures were 20% and 17% respectively, (3% difference in favor of tenoxicam, $P = 0.58$, 95%CI 9% to –2%). Two patients in the placebo group and three in the tenoxicam group had a discharge status score of 3 (difference 1.1%, $P = 0.68$), while the remainder of those unwell had scores of 2. No scores of 4 or 5 were recorded.

Table 5. Health Status and Treatments required with 95% Confidence Intervals for the differences observed. For subject numbers at each analysis see Figure 1.

Outcome	Placebo	Tenoxicam	P value (95% CI)
Health status at discharge >1	25 (30%)	31 (37%)	0.41 (21% to –7%)
Health status at 4-6 weeks >1	16 (20%)	14 (17%)	0.58 (9% to –20%)
Median treatments required to discharge (range)	3 (1 - 8)	2 (1 - 6)	0.01 (0 to 1)
Subjects requiring more than 2 treatments	53 (61%)	35 (40%)	0.01 (6% to 34%)

There was a significant difference in the number of compressions required to achieve discharge criteria. Tenoxicam subjects required fewer treatments, (a median of 2 versus 3 treatments, $P = 0.01$). 40% of subjects in the tenoxicam group required more than two treatments to discharge, while 61% of the placebo group required more than two treatments (21% difference in favor of tenoxicam, $P = 0.01$, 95%CI 6% to 34%).

Subgroup analysis by presentation severity grade was made for both health outcomes and number of treatments required. These are summarized in Table 6.

Table 6. Outcome analyses by admission severity grade with 95% confidence intervals for the differences observed.

Presentation grade	Outcome	Placebo (%)	Tenoxicam (%)	P value (95% CI for difference)
One	Discharge status > 1	2 (13%)	5 (28%)	0.41 (-41% to 15%)
	Final health status >1	2 (14%)	1 (5%)	0.57 (36% to –29%)
	Median treatments (range)	3 (1-3)	2 (1-4)	0.20 (0-1)
	> 2 treatments	8 (53%)	4 (21%)	0.08 (60% to –1%)
Two	Discharge status >1	10 (22%)	20 (36%)	0.19 (-31% to 4%)
	Final health status >1	10 (20%)	11 (20%)	0.92 (-15% to 16%)
	Median treatments (range)	3 (1-6)	2 (1-6)	0.15 (0-1)
	> 2 treatments	34 (60%)	25 (45%)	0.19 (48% to –18%)
Three, four and five	Discharge status >1	9 (53%)	5 (36%)	0.27 (37% to –21%)
	Final health status >1	4 (31%)	2 (14%)	0.66 (37% to -21%)
	Median treatments (range)	4 (1-8)	2 (1-6)	0.14 (0-2)
	> 2 treatments	13 (72%)	6 (43%)	0.15 (58% to –5%)

Due to the small numbers enrolled with high severity scores, grades 3, 4 and 5 have been combined. There were no significant differences on any of these analyses, although the trends suggested the difference in treatment numbers required was preserved across all severity grades.

There were no significant differences in the proportion of subjects with an outcome score >1 at discharge or review when analyzed for initial compression treatment schedule (USNTT6 162 subjects, outcome score >1 32% at discharge, 15% at 4-6 weeks; USNTT5 15 subjects, outcome score >1 13% at both times; other tables 3 subjects, outcome >1 33% at both times. Overall Chi^2 for difference 2.17, $P = 0.34$ at discharge, Chi2 0.70, $P = 0.7$ at 4-6 weeks).

DISCUSSION

We have reported a clinical study on the adjunctive use of the NSAID tenoxicam in the treatment of DCI, and from it we draw three conclusions. First, the routine administration of tenoxicam does not significantly influence the interim or ultimate health outcome following recompression and HBO_2 for DCI. Second, the administration of tenoxicam favorably influences the number of recompressions required to achieve discharge criteria. Our results suggest there is a 33% reduction in the relative risk of a patient requiring more than two compressions (from 61% to 40%), so that for every 5 patients treated for DCI, we can expect one patient to require at least one less compression (NNT 5, 95%CI 3 to 18). Third, there is no evidence from this study

to suggest that administration of an NSAID results in any significant harm to the patient in short or medium term.

Given that patient compliance was largely measured by self-reporting in this study, it may be that a significant proportion of subjects did not take the medication as prescribed. If so, while we may in fact have underestimated the efficacy of tenoxicam in these subjects, it is likely that our estimate accurately reflects effectiveness in actual clinical practice.

There are, however, several potential problems with this study. Of the subjects, 9% at final follow-up were formally classified as not suffering DCI. There is a possibility, therefore, that this trial demonstrates only that non-DCI injury responds to NSAID administration and that the clinical course of 'true' DCI cases is not influenced. We believe this is unlikely because the treatment sparing effect seems preserved across all grades of severity. Moreover, this distinction is irrelevant because a clinician faced with a patient in whom DCI is likely will be in the same position as the investigators in this study and can expect similar results.

The great majority of subjects presented with a clinical diagnosis of musculoskeletal or mild neurological disease. While the analysis of more serious illness suggests the treatment-sparing effect is likely to be uniform across all grades of presentation, the small numbers for analysis of grades 3, 4 and 5 give us less confidence that this is so. Confirmation of any effects at the magnitude suggested by this study will require further investigation, but could only be achieved through a large trial with approximately 100 such serious cases to show an effect on treatment numbers, and over 1,000 cases to show improvement in final outcome. Given our experience over a 5-year period in the present investigation, such studies would require many participating centers, would be very time-consuming and are unlikely to be undertaken.

It has been suggested that the administration of NSAIDs in the clinical context of pain-only DCI may resolve symptoms, thereby masking important pathologic processes and preventing adequate recompression treatment. It was not our purpose to propose tenoxicam as an alternative therapy to recompression and HBO_2. Therefore, our protocol deliberately recommended the standard recompression treatment approach as described by Moon and Gorman, utilizing an initial compression to 2.8ATA (18msw) on oxygen and subsequent follow-up treatments as clinically indicated (9). While a small proportion of our subjects (10%) were compressed initially on other than USN TT6, we cannot draw any conclusion regarding the appropriate choice of treatment table from this study. Again, we argue that this trial reflects clinical choice and is likely to predict response in the field.

Despite the apparently uniform effect of tenoxicam across all grades of severity in this study, we cannot exclude the possibility that pain rather than neurological manifestations determined the need for ongoing treatment in some of the more serious cases. Consequently, the simple analgesic effect of tenoxicam might explain the reduction in treatment numbers. The data from this study can neither support nor reject this possibility. Under these conditions of adjunctive use, however, the recompression therapy avoided has not resulted in any significant change in health state at either interim or final assessment. It might be argued that the rate of late complications of DCI, particularly dysbaric osteonecrosis (DON), may be increased as a consequence. However, given the very low rates of DON, the poor correlation with a history of DCI and the recommendation of at least one USN TT6 to these patients, this possibility seems remote.

There was no specific pharmacodynamic rationale for the choice of tenoxicam for this study. Tenoxicam is a typical NSAID of the oxicam group (which includes piroxicam). It blocks both COX-1 and COX-2 isoforms and has an intermediary IC_{50} COX-2/COX-3 ratio (27). It is

therefore potentially nephrotoxic, particularly in patients with compromised renal function and the elderly. Despite this, such drugs are used commonly for rheumatic disorders and have been investigated extensively (28). A recent randomized controlled trial of tenoxicam 20mg intravenously immediately pre-operatively for elderly patients having major gynecological surgery, failed to demonstrate significant renal dysfunction, increase in blood loss or increase in bleeding time (29).

Tenoxicam did have certain useful pharmacokinetic properties in this study. With 100% absorption orally, and an elimination half-life of approximately three days, it allowed a once daily oral regimen with high patient compliance. It is completely metabolized to inactive compounds excreted in the urine and feces (30). There is an analgesic ceiling effect, above which increasing dose results only in increasing toxicity without addition analgesia and the dosage regimen used here is appropriate in this context (31).

We believe the results of this study justify the routine administration of a non-specific NSAID as an adjunct to recompression and HBO_2 for DCI. While this approach is unlikely to lead to improvement in health outcome, such treatment will shorten the course of recompression required for some patients, with cost savings to the facility and patient and with no demonstrable patient harm.

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