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Retrospective Review

A Predictive Model for Intrathecal Opioid Dose Escalation for Chronic Non-Cancer Pain

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Background: Tolerance is defined as a phenomenon in which exposure to a drug results in a decrease of an effect or the requirement of a higher dose to maintain an effect. The fear of a patient developing opioid tolerance contributes regularly to the stigmatization and withholding of intrathecal opioid therapy for chronic pain of non-cancer origin.

Objectives: The aim of this study was to describe the intrathecal opioid dose escalation throughout the years in chronic non-cancer pain patients. A secondary objective was the development of an intrathecal opioid dose predictive model.

Study Design: Retrospective assessment of medical records.

Setting: Department of Pain Management, Russells Hall Hospital, Dudley, United Kingdom.

Methods: Medical records were reviewed and pump refill notes screened from the date of implant through November 2010 for 31 patients undertaking continuous intrathecal opioid therapy. All the patients included had undertaken a minimum of 6 years of intrathecal therapy when the data were collected.

Results: Significant increases in the intrathecal morphine dose were verified between follow-up at one year and all subsequent observations, $F(2.075, 62.238) = 13.858$, $O < 0.001$, but ceased to be significant from year 3 onwards, indicating stability of the morphine dose, $F(3, 90) = 2.516$, $P = 0.63$. A model that accounts for 76% of the variability of morphine doses at year 6 based on year 2 assessment combined with duration of pain prior to initiation of intrathecal therapy was developed: year 6 dose = -0.509 + (1.296 x [year 2 dose]) + (0.061 x [duration of pain]).

Limitations: Retrospective study.

Conclusion: The opioid dose escalation observed throughout the years was modest and not significant following year 3 of therapy. The model developed has the potential to assist the physician in the identification of a need for alternative treatment strategies. Furthermore, since many of the pump replacements are performed prior to year 6, it can also assist in the informed decision of the benefits and risks of the maintenance of this therapy.

Key words: Chronic pain, non-cancer pain, intrathecal opioid therapy, opioid dose escalation, predictive model.

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The concepts of addiction and dependence are often associated with tolerance. Dependence can be divided into physical and psychological. An individual is physically dependent on a substance when an abstinence syndrome or withdrawal occurs after sudden dose reduction, cessation of therapy, or administration of an antagonist drug (1). Psychological dependence can be considered as a component of the

addiction concept because it implies the craving of a substance for its psychological effects (2). Addiction is characterized by the compulsive use of a substance (despite harm), drug seeking behaviors, and a high tendency to relapse following withdrawal (1,3). In the clinical setting, addiction is also associated with noncompliance with suggested opioid changes (4). However, opioid addiction is more common outside a pain clinic setting. In a recent systematic review, the observed signs of opioid addiction in pain management patients corresponded to 0.14%, indicating a low rate of opioid addiction development (5). The authors considered that the low rates of addiction should only be generalized to patients without a history of addictive/abusive behaviors. Despite situations where extremely high doses of intrathecal opioids were administered, only one study has reported a possible development of opioid addiction in the form of drug seeking behavior (6).

Tolerance refers to a phenomenon in which exposure to a drug results in a decrease of an effect or the requirement of a higher dose to maintain an effect (1). Tolerance to opioids is characterized by a shortened duration and decreased intensity of the effects caused by depression of the central nervous system such as analgesia, euphoria, or sedation (1). Pharmacodynamic tolerance refers to adaptive changes which take place within the systems affected by the drug, such as changes following drug administration in receptor density or receptor sensitivity, so that response to a given concentration of the drug is reduced (7).

Animal studies have demonstrated opioid tolerance to be pharmacodynamic, time and dose dependent, receptor specific, and reversible if the agonist is removed (8,9). The predominant pharmacodynamic tolerance described in animal studies should not be considered as the cause for loss of analgesia in humans unless there is no evidence for pharmacokinetic or learned tolerance (2). Unlike the animal models of tolerance, human pain is more complex and there are several factors that may lead to a decrease in the analgesic effect of a drug. Psychological processes such as anxiety, depression, mood, and cognition influence pain perception and may lead to a worsening of pain (2,10,11,12). A contributor for an increase in pain perception is also the progression of a condition or its associated factors, such as an increase of activity in central or peripheral nociceptive pathways (2).

Intrathecal drug delivery (IDD) systems are a last resort treatment for the management of severe chronic non-cancer pain due to their invasive nature, high initial cost, concerns about long-term opioid use, and the possible complications related to the procedure; however, it appears to be an effective therapy. The use of IDD systems should only be considered at the end of a long treatment continuum after all possible alternative therapies have been tried and failed due to inadequate pain relief or intolerable adverse effects (13,14). Despite high initial costs, IDD systems are a cost-effective treatment for the management of chronic non-cancer pain (15,16,17) and recent studies support the long-term effectiveness of IDD systems following 3 years of treatment (18) and a mean of 13 years of therapy (19). Patients with chronic non-malignant pain have the potential for long-term survival and therefore adequate pain control is paramount to this population. The investigation of opioid dose escalation assumes particular importance because the possibility of tolerance development is a commonly used reason to withhold the use of opioid treatment until an undeniable need (2).

The primary purpose of this study was to investigate the intrathecal opioid dosage escalation of a cohort of patients undertaking IDD therapy for the management of chronic pain of non-cancer origin. A secondary objective was the development of an intrathecal opioid dose predictive model.

Methods

Patients

Thirty-one consecutive patients undergoing continuous intrathecal opioid delivery by implanted reservoir administration for chronic non-malignant pain at Russells Hall Hospital Pain Management Department were included in the study. The sample consisted of 19 women (61.3%) and 12 men (38.7%). Their average age at the time of IDD system implantation of 48 ± 1.5 years (range: 30-63). The average duration of pain prior to IDD was 12 ± 1.4 years (range: 2-35). All the patients had undergone IDD therapy for at least 6 years when the data were collected.

The pain syndrome the majority of the patients (74.2%) experienced was likely to be nociceptive as the result of degenerative spine disease, mechanical low back pain, or osteoarthritis. Three patients (9.7%) had neuropathic pain as the result of complex regional pain syndrome type II and 5 patients (16.1%) suffered from mixed nociceptive-neuropathic pain, including failed back surgery syndrome caused by multiple spinal operations. For the purpose of comparison, the pain to-

pography was divided into low back and other. For most patients, the site of pain was the lower back (48.4%), while in the other group the pain was localized in the abdominal area, knee, or back pain radiating to one or both legs. In all cases, the catheter entry was in the lumbar spine and catheter tip positioned in the thoracic area, most commonly T10.

Data Collection

A longitudinal retrospective assessment of medical records was performed and pump refill notes were screened from the date of implant through November 2010. Intrathecal drugs administered and intrathecal opioid dose (mg/d) were recorded. To try to attain optimal pain relief, some patients had additional drugs besides morphine added to the intrathecal medication, such as bupivacaine (87.1%), clonidine (35.5%), and baclofen (19.4%). Only 12.9% of those with nociceptive pain relied on morphine alone. Throughout the duration of treatment, when attending for a pump refill, the patients were asked if the pain was under control or if new symptomatology had emerged. Between follow-ups, a help line managed by pain management nurses was available for urgent situations. If pain relief was not optimal, aspects such as pain level, function and new symptoms would be examined during follow-up and the physician would either increase the intrathecal opioid dose, try an additional medication, or investigate for pump-related complications or granuloma development. All physicians involved in the care of IDD patients at this center followed the same practice and criteria. Yearly opioid dose averages were computed for each patient from the time of implant until last refill from June through November 2010. The data were collected as part of a retrospective clinical audit, and therefore informed consent and ethical approval was not required according to institutional guidelines and the National Research Ethics Service (20).

Data Analysis

The data did not follow normal distribution and attempts to transform the data were not successful. As analysis of variance is robust to violations of normality, repeated-measures analysis of variance were performed to investigate changes in opioid dose throughout the treatment period. Assumption of sphericity was verified through Mauchly's test. If the assumption of sphericity were violated, the degrees of freedom associated with the analysis needed to be corrected. Degrees of freedom were corrected using Greenhouse-Geisser estimate of sphericity, when the variances of the differences between levels were significantly different. Opioid dose changes were controlled for gender, age, duration of pain prior to IDD, topography of pain, type of pain, IDD system replacements, and administration of intrathecal adjuvant medication.

Stepwise multiple regression analyses were used to evaluate the significance of the variables mentioned above in a model predicting the intrathecal morphine dose at year 6 based on the dose at year 2. Shapiro-Wilks test was carried out to investigate if the unstandardized residuals data were normally distributed, therefore examining the validity of the model derived from the multiple linear regression. Since the variable type of pain was divided into 3 categories, the variable was recoded to create 2 dummy variables with 2 categories each in order to carry out the linear regression.

Data are reported as mean ± standard error of mean. Statistical significance was judged to be at the 5% level. Statistical tests were performed using SPSS software, version 17.0 (SPSS Inc., Chicago, IL).

Results

Assumption of sphericity were violated ($P < 0.001$), therefore the degrees of freedom and the *P*-values presented correspond to Greenhouse-Geisser correction. Gender (F [1.812, 39.874] = 0.623, $P = 0.526$), age at time of implant (F [1.812, 39.874] = 0.185, $P = 0.811$) and duration of pain prior to IDD system implantation (F [1.812, 39.874] = 2.389, $P = 0.109$) did not have a significant effect on the intrathecal opioid dose. The addition of adjuvant intrathecal medication did not have a significant effect on the dose throughout the years, F (1.812, 39.874) = 0.220, $P = 0.782$. The morphine dose was not influenced by the location of pain (F [1.812, 39.874] = 0.227, $P = 0.776$) or type of pain (F [4.074, 57.032] = 0.858, $P = 0.422$).

Although not statistically significant, it was observed that neuropathic pain patients required lower doses throughout the duration of therapy (Table 1). At baseline, the opioid doses were approximately the same among the different types of pain. At 2-year follow-up, differences start to be evident, remaining throughout the duration of the study.

During the study period, 12 patients did not need a replacement of the IDD system. Pump replacements were performed at a mean follow-up period of 59 ± 3.72 months (range: 17-84). None of the patients required more than one IDD system replacement. The intrathecal opioid dose was not significantly affected

Table 1. *Mean morphine doses during intrathecal morphine therapy according to type of pain*

	Opioid dose (mg/day)			
Type of pain (n)	**Baseline***	**2 year follow-up***	**4 year follow-up***	**Last follow-up***
Nociceptive (23)	0.84 ± 0.17	2.43 ± 0.32	3.11 ± 0.52	3.5 ± 0.49
Neuropathic (3)	0.82 ± 0.23	1.63 ± 0.69	1.82 ± 0.59	1.82 ± 0.51
Mixed (5)	0.66 ± 0.17	3.55 ± 0.75	5.28 ± 1.40	4.51 ± 1.19
Total (31)	0.81 ± 0.13	2.53 ± 0.28	3.34 ± 0.47	3.51 ± 0.42

* Mean ± SEM

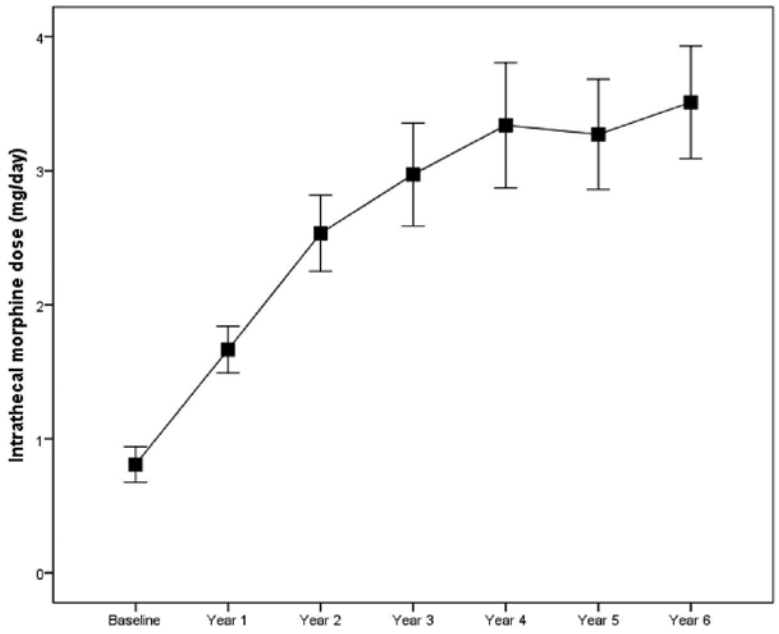

Fig 1. *Intrathecal morphine dose over the study period. Error bars represent standard error of mean.*

by the need of an IDD system replacement F (1.812, 39.874) = 2.562, P = 0.095. In accordance with the average duration of therapy until an IDD system replacement surgery was required, a reduction in the opioid dose can be observed in Fig. 1 between years 4 and 5.

Significant increases in the intrathecal morphine dose were verified between follow-up at one year and all subsequent observations, F (2.075, 62.238) = 13.858, $P < 0.001$. From year 3 onward, no significant differences were observed with subsequent doses, F (3, 90) = 2.516, P = 0.63.

Multiple linear regressions were used to analyze the relationship between yearly morphine doses. The results of the regression analysis indicated that the morphine doses of year 2, together with the duration of pain, were significant predictors of the intrathecal opioid doses at year 6 (year 6 dose = -0.509 + [1.296 x (year 2 dose)] + [0.061 x (duration of pain in years)]. Although the duration of pain initially was found not to have a significant effect on the intrathecal opioid dose throughout the duration of the study, it was verified that it improved this model, albeit modestly. Gender (P = 0.419), age at time of implant (P = 0.2), topography of pain (P = 0.46), type of pain 1 (P = 0.406) and type of pain 2 (P = 0.544) were not significant predictors for the model. This model accounted for 76% of the variability of morphine doses at year 6 based on year 2 assessment. The residuals follow normal distribution (P = 0.809), which indicates that the assumptions for regression were met and confirms the validity of the model.

Discussion

In this sample, a slow increase in opioid dose was observed. Statistically significant increases were observed on a yearly basis from baseline up to year 3, but the intrathecal opioid dose increase ceased to be significant from the third year onward, indicating stability. For safety reasons, the initial intrathecal opioid dose was low. In subsequent refills the dose was titrated until the patient obtained satisfactory pain relief. Because the increase in each review also tended to be modest due to safety reasons, it could have taken several reviews to achieve suitable pain relief. This explains the initial continuous and significant increase up to year 3 and the modest increase after that period.

The average intrathecal dose of 3.51 mg/d at last follow-up (year 6) was lower than previously reported average doses of 7.42 mg/d at 29.14 months (21); 9.6 mg/d at year one (22), and 12.2 mg/d at year 3 (18). An approximate opioid dose of 4.7 mg/d has been reported, although at an average of 3.4 years (23). These disparities in doses administered suggest diversity in practice among departments administrating this therapy. Nevertheless, previous surveys have reported modest morphine dose escalations in patients with chronic non-malignant pain (22,23).

There are several factors that may have contributed to the modest dose escalation throughout the duration of therapy. To some extent, the small increase verified in the intrathecal opioid dose may be related to the fact that the majority of the patients (87.1%) were receiving intrathecal bupivacaine in addition to the intrathecal morphine. The addition of intrathecal bupivacaine has been effective in keeping the intrathecal morphine dose low in the treatment of cancer pain (24,25) and non-cancer pain (26) as well as preventing the potential side effects of high doses of intrathecal morphine. Drugs that have the potential to reduce the addiction liability of opioids or enhance the analgesic efficacy of opioids, as well as having analgesic properties on their own, may be useful as adjuvant therapies in combination with opioids (27). This supports the suggestion that the use of adjuvant analgesics appears to contribute to an opioid-sparing effect. Other factors could also be relevant, such as the continuous care by the same team, in the same context, allowing the establishment of a doctor/nurse-patient relationship in a safe environment for the patient.

Contrary to what was expected, the opioid dose administered to neuropathic pain patients was lower than the dose received by the nociceptive pain patients. In accordance with our results, previous literature has reported lower opioid doses administered to neuropathic pain patients when compared to the dose administered to patients with nociceptive pain (21,23). The lower dose in patients with this pathology may also be related with the administration of adjuvant medication. Neuropathic pain has shown to be responsive to intrathecal therapy, but opioids alone may not always be sufficient to control it (28). The reduced sensitivity of neuropathic pain to opioids may be the result of a decreased expression of μ-opioid receptors in dorsal root ganglia neurons as a consequence of nerve injury (29).

There was no evidence of opioid addiction or abuse in the investigated patients. The screening and exclusion of patients with a history of addictive behaviors prior to the intrathecal morphine trial could have contributed to this outcome. The cerebrospinal fluid has a limited capacity to distribute intrathecally administered morphine away from the catheter tip (30,31) which besides having implications on the efficacy of the intrathecal therapy, also means that only a very small amount of the medication would reach the supraspinal regions. It is known that the opioid regulation of pain involves μ-opioid receptors in both spinal and supraspinal regions of the central nervous system (32). The amygdala, whose nuclei have no direct association with analgesia, has the greatest abundance of opioid receptors in the brain; the receptors in this area are likely to be associated with the influences of opioids on emotional behavior (33). It seems plausible that the development of addictive behaviors as a consequence of intrathecal morphine therapy is even more remote than with the use of systemic opioid therapy because of the much lower dose and spinal region of opioid receptor activity (34).

It is important to note the limitations of this study. Pain ratings were not requested on a regular basis to verify if a change or deterioration in pain occurred. A longitudinal study with a mean follow-up of 13 years of IDD therapy conducted in the same center demonstrated a small, non-significant increase in the pain ratings between prospective assessments following IDD system implantation (19). This increase in pain could be due to a progression of the disease or a decrease of therapy effectiveness (tolerance), leading to the small increases observed in the morphine dose.

Oral opioid medication was not collected from the notes. At this center, rescue oral opioid medication has been provided to patients on an individual basis, for occasional flare-ups. The average duration of pain

prior to IDD was 12 years. Prior to implantation of the IDD system, all these patients had tried and failed more conservative treatments, including oral opioid medication, with little or no benefit or intolerable side effects. The effective rescue medication dose is a fraction of the effective intrathecal dose. Hence, systemic medication as well as other interventions that might have been undertaken during the study period would only be sporadic to cope with flare-ups, and would therefore have limited effect on the results verified. Providing additional oral medication to patients may improve their psychological well being as well as an improvement in effective pain control. There is no evidence of a correlation between reduction in pain intensity and the intake of additional oral medication (21,23).

This model assumes particular importance because it can predict 76% of morphine dose variability at year 6. Since the pump battery life usually ranges between 48 to 60 months (16,35), an informed decision can be made taking into account the risks and benefits of continuing intrathecal opioid therapy. Statistically, year 5 would provide a more accurate model. However, we considered that for clinical practice, it would be more beneficial to be able to estimate the opioid dose at an earlier stage. The possibility of anticipation of the opioid dose could also lead to consideration by the physician of alternative biopsychosocial treatment strategies. Examples of alternatives are the addition of adjuvant drugs to the intrathecal mixture and physical or behavioral approaches (36,37). It is not the authors' intention to state that the future treatment of a patient should be decided based on a mathematical model. This model should be seen as an auxiliary tool assisting a physician's work.

Therapy strategies differ across treatment centers and can explain much of the variation in the administered intrathecal opioid dose and escalation. Therefore, the applicability of this model to other centers needs to be tested. A large, international, multicenter study could have the potential to develop a model applicable to the majority of centers where intrathecal drug delivery is administered.

Conclusion

The opioid dose escalation observed was not a limiting factor for this therapy as the increase throughout the years was modest. Due to the duration of the study and the small dose increases verified, it seems that concerns about development of tolerance do not justify the delay or withholding of intrathecal opioid therapy for chronic non-cancer pain patients.

The evaluation of the intrathecal opioid dose throughout a 6 year period allowed the development of a model. This model accounts for 76% of the variability of the opioid dose at year 6 based on the dose of year 2 combined with the duration of pain prior to initiation of intrathecal therapy. This has significant clinical implications. It can assist the physician to identify the need of an alternative treatment strategy. Moreover, since many of the pump replacements are performed prior to year 6, it can assist in the informed decision of the benefits and risks of the maintenance of this therapy prior to replacement surgery.

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