Intraventricular Morphine Therapy In Cancer Pain

KAYA KILIÇ, ALAIN CZORNY, BEHİÇ TÜMER, MAHİR TEVRÜZ

Haydarpaşa Numune Hospital, Department of Neurosurgery, İstanbul, Türkiye (KK, BT, MT)
Service de Neurochirurgie, CHU e Besancon - France (AC)

Abstract : The authors study the effectiveness and complications of intraventricular morhphine therapy in the treatment of preterminal cancer pain and compare it with other central and systematic administarions of morphine.

In this series of 35 patients, intraventricular morphine therapy was used when complications of peridural morphine therapy develop or when high dose morphine application by the systematic method had no effect. The quality of analgesia was assessed as "perfect" in 82 % of the cases. The average hospitalizaion period was 2 days. All other systematic sedatives, analgesics and antidepressants were stopped and the initial dose of 0.1 mg/day of morphine never subsequently exceeded 0.2-5 mg)day.

Key Words: Intraventricular morphine. Pain. Cancer.

INTRODUCTION

Morphine therapy is used as the W.H.O. also suggests, after non-opioid analgesics and weak opiodis (Codeine) have been tried and a systematic method used in the administration of morphine: per os, I.M., I.V. or s.c. The dose is increased once tolerance develops and as this becomes insufficient or side effects of the morphinotherapy develop, other "central" methods are employed i.e. epidural, intrathecal, intraventricular. The morphine reservoir has made such use of morphine more widespread.

MATERIAL AND METHODS

Our study examined the results of intraventricular morphine therapy in intractable cancer pain in 35 patients in the preterminal stage. The sex distribution of the patients in the series showed a clear majority of males: one female compared with 34 males. We were not able to explain this difference and have not encountered anything sımılar in the literature.

Table I shows the distribution of the primary neoplasm in 35 cancer patients.

Table I. Dustribution of Primary Neoplasm:

DISTRIBUTION OF PRIMARY NEOPLASM:
HEAD AND NECK: 21
LUNGS: 11
PROSTATE: 2
BREAST: 1

Intraventricular morphine therapy was employed in all 35 when:

– Systematic morphine was insufficient regardless of the high dosage,

– One of the known complications of peridural morphine therapy was encountered (inflammation, infection, rejection of the catheter) or

– When preterminal cancer pain did not allow surgical interception of
the nociceptive tractus (cordotomy, radicotomy).

Table II shows the treatment and the dosages tried on the group before the morphine reservoir. In 5 of the 10 patients fitted the epidural catheter, the catheter was rejected. The daily morphine dosage given to these patients varied between 6-24 mg.

Table II. Treatments And Dosages Tried Before The Morphine Reservoir:

EPIDURAL CATHETER (6 mg-24 mg/day morphine)	: 10 cases
MORPHINE SYRUP (30 mg-240 mg/day) and/or DEXTROMORAMIDE (3-20 TABLETS/DAY PALFİUM):	19 cases
LEVOMEPROMAZINE (Nozinan) or FLUNITRAZEPAM (Rohypnol) or PENTAZOCINE (Fortal) and/or DEXTROPROPOXYPHENE (Propofan)	: 6 cases

Major analgesics such as morphine syrup and dextromoramide proved ineffective in 19 cases although given in high doses.

Morphine reservoirs were placed in the other six patients when numerous sedatives, antalgics and neuroleptics proved in effective in stopping the pain. When changing from systematic morphine therapy to the intraventricular morphine reservoir, 0.1 mg of intrathecal morphine chlorhydrote was given and changes in the pain of the patient were observed. It was discovered that pain responding to intrathecal morphine benefits from the morphine reservoir.

The technique for placing the intraventricluar morphine reservoir is identical with that used in ventricular puncture: It is based on puncture of the frontal horn of the lateral ventricle under sterile conditions and neuroleptanalgesia or via a burr hole drilled 3 cm in front of the coronal suture and 3 cm lateral to the midline. The drug placed in the reservoir is 0.1 mg/ml concentration morphine chlorhydrate. The total volume should not exceed that of the reservoir, namely 3 ml.

RESULTS

The inital dosage in our group was relatively low, usually 0.1 mg/day, and between 0.2-5 mg/day at the and of the treatment.

The longest and shortest effective treatment lasted 195 and 3 days respectively with an average of 51 days.

Table III shows the early complications encountered in 35 patients. The quality of analgesia was assessed as "perfect" in 29 cases (82 %): no pain was observed in these patients even though all antalgics, sedatives and antidepressants had been discontinued.

Table III. Early Complications Encountered In 35 Patients

– Respiratory depression	: 0
– Retention of urine	: 0
– Convulsions	: 2
– Infections	:2
– Regressive hemiparesis	: 2
– Haematoma	: 0
– Mild intoxication (myosis, hallucination)	: 2
– EXITUS	: 0

The average period of hospitaliazion was 2 days, after which the patients were sent to the first department of reference and then discharged to their homes. Subsequent injections were administered either by a nurse or one of the family after detailed instructions.

The side effects of a method used to treat pain in cancerology should be minimal and the analgesic efficiency maximal. Thus, intraventricular morphine therapy is superior to other methods in many ways:

– The analgesia was highly superior in terms of duration and quality: the intraventricular method provided analgesia with 2 times less morphine than the intrathecal and 5 times less than the epidural method.

In some cases 1000 times less morphine was needed than that used in the systematic method. Analgesia was observed throughout the entire body, especially on the face, thus it is very useful in Head and Neck cancers.

– The minimal and even lack of side effects provide the patient with physical and psychological comfort. "Respiratory depression" which is a feared complication of the intrathecal method was not observed even in its weakest form.

– It is possible to continue the treatment at home because of the absence of respiratory depression, the effectiveness of small doses and few other side effects.
– Injections into the reservoir with hypodermic needles are painless, easily applied and do not interfere with the autonomy of the patient. The bath and dressing problems of a permanent peridural catheter are absent.

DISCUSSION

Mu, delta, kappa, epsilon and sigma receptors sensitive to morphine are found on the medulla spinalis and the brain stem. These are especially dense:

– On the substantia gelatinosa of Luigi Rolando situated in the dorsal horn of the medulla spinalis,

– In the periventricular and periaquaductal gray matter and

– In the cingular, fronto-basal and hypothalamic regions of the limbic system. (8, 9, 17, 18, 21, 22).

Morphine directly applied to the central nervous system reaches these receptors along the shortest route. Furthermore a big portion of it is not metabolized and inactivated in the liver like morphine applied systematically thus "longer and more effective" analgesia is provided with "much smaller doses". (3, 4, 5, 7, 12, 13, 14, 15, 19).

The scarcity of side effects such as diuresis, pruritus, constipation, bradycardia, hypertension and nausea and especially absence of respiratory depression are among the advantages of intraventricular morphine therapy. The reason for the higher frequency of respiratory depression in intrathecal morphine therapy is that the flow direction of the C.S.F. causes the bulboprotuberential effect to be more intense and faster.

During the central and peripheral stages of pain, morphine takes effect by increasing the analgesic power of the enkephalines (1, 6, 10, 11). The central effect mechanism is by activation of the bulbo-spinal serotoninergic descending inhibitor fibrils. Periaquaductal gray matter is rich in enkephalines and opium receptors hich are connected to the beginning of the serotoninergic inhibitor pathays in the brain stem. this descending pathay activates the interneurons in the substantia gelatinosa of Rolando and thus prevents the release of neurotransmitter of pain, subtance P by the thin C fibres.

In the periphery, like the enkephalines, morphine is attached to the morphine receptors in the medulla spinalis substantia gelatinosa and prevent the release of substance P. The accepted opinion is that of knon morphine receptors, the mu is related to the antalgic effects and delta and kappas to other side effects.

Intraventricular morphine in small doses blocks the mu receptors with an antalgic effects. But the side effects are slight because it does not block the delta and kappa receptors. On the other hand, in morphine treatment by other methods doses to block all the receptors are needed and the risk of side effects and respiratory depression is increased. Although the percentage of pain occurrence varies depending on the stage of the tumour, a global pain ratio of 51% has been reported.

Pain frequency is increased to an average 75 % in advanced terminal patients (2). Relief from pain should be regarded as the most natural right of all cancer patients and a pain therapy respecting this right should be used. Drugs are the basis of the cancer pain treatment Strong opioids such as morphine are found in the last step of the three-step analgesic treatment suggested by the .H.O. Pain is no longer regarded as a "rule of fate" and physicians are approaching this subject in a more scientific manner, but the manner in hich stupefacients are used and the number of patients benefitting from them is still insufficient. An analysis of 12 studies done in developed countries involving 2600 patients has shown that over 50% of the patients do not receive sufficient pain treatment (16).

CONCLUSION

Cancer pain is intense, organic, and constant through continuous hyperstimulation and has important psychological consequences. Pain surgery can be considered for patients with paint hose life expectancy is long enough (at least 1 year) to justify it. (6, 20). For this reason, intraventricular morphine is an effective and low risk alternative to surgical interruption of pain pathways in preterminal cases. It should be considered especially in cases here classical methods prove ineffective in cancer pain of supradiaphragmatic locatization. However this treatment should be employed before the terminal stage and especially before dependency on opioids develops. In smilar pain of infradiaphragmatic cancer, our choice is a subcutaneous morphine reservoir with a peridural catheter. When the required conditions are met, placement of an intraventricular morphine reservoir seems to be the preferred method for the following reasons:

1. The quality of analgesia
2. The perfect tolerance
3. Comfort
4. The low dosage of required morphine and
5. The scarcity of side effects.

Correspondence : Kaya Kılıç M.D.
Numune Hospital,
Nöroşirürji Kliniği
Üsküdar-İstanbul/Türkiye

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