RECENT TRENDS IN THE PERI-SURGICAL USE OF CONTINUOUS EPIDURAL ANESTHESIA IN ELDERLY PATIENTS WITH VULVAR NEOPLASIA

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SUMMARY

The experience acquired with the use of epidural morphine during the peri-operatory period confirms the efficacy and safety of the method also in elderly patients with neoplasia and multiple pathologies of various etiology.

Several electrophysiological data suggest that the main action of local anesthetics involves the direct depression of membrane permeability to Na^+ ([1, 2]). This reduction in sodium conduction prevents normal depolarization in response to applied stimuli ([3]), so that propagated impulse generation does not occur, and in effect a condution block follows. The underlying mechanism is related to the interaction of the local anesthetic with specific membrane lipoprotein receptors, which are present on the internal side of the plasmatic membrane in correspondence with the sodium channels ([4]). The possibility of passage through the channel is conditioned by the physico-chemical properties of the local anesthetic itself, such as molecular weight, lipid solubility, pK and environmental pH. Under equal conditions, the non-ionized form which lacks charge and is therefore hydrophobic, presents a greater diffusability. The state of the acid-base balance may thus be important in determining the clinical action of local anesthetics. Alkalosis brings about a rapid induction of the anesthetics as well as a greater profundity. On the contrary, injection of local anesthetic into inflamed tissues where pH is reduced, brings about an insufficient degree of anesthesia due to the lesser quantity of uncharged anesthetic.

A specific clinical problem that may be related to topical modifications in H^+ concentration is constituted by the phenomenon of tachyphylaxis, a state of rapid tolerance that is frequently observed following continuous or repeated administration of local anesthetics in the subarachnoid or epidural space ([5, 6]). Although the etiology is not completely ascertained, there are data which support the hypothesis that tolerance development following repeated intrathecal administration of anesthetic may be related to modifications in the H^+ concentration in the cerebrospinal fluid (CSF) ([7]); a reduction in pH brings about a relative decrease in the

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non-ionized form of the local anesthetic which translates clinically into a reduced analgesic response.

The aspecificity of the block produced by local anesthetics conditions the modification in normal function of the extranociceptive fibers too: paresthesias, muscular weakness, and neurovegetative disorders (hypotension) are the obvious consequences of epidural anesthetic block, and more still of subarachnoid block.

Recent studies ([8, 9, 10, 11, 12]) have demonstrated that narcotic analgesics are able to produce an intense and prolonged segmentary analgesia when they are injected into subarachnoid or epidural space. Although the mechanism of action is not yet completely known ([13]), it is thought, nevertheless, that the opiates mediate the activity of Roland's gelatinous substance directly by decreasing substance P release, a neurotransmitter involved in the function of the first nociceptive synapse ([14]). The importance of the activation of the medullary receptors for the opiates has been confirmed by studies conducted on paraplegic volunteers ([13]). Following i.v. morphine injection, these subjects showed a rapid and profound depression of the nociceptive reflexes in flexion while the monosynaptic reflexes were not significantly altered, not even at higher doses. These results agree with the report of Le Bars *et al.* ([15]) who observed a sharp decrease of the activity of the V lamina cells of Rexed (neurons originating the spinalthalamic pathway), following nociceptive stimulation, but no influence on response to tactile stimuli when morphine was i.v. administered to spinal cats. Therefore, it seems reasonable to state that morphine may block the nociceptive messages totally and selectively at the spinal level without affecting the tactile responses. The specificity of its action is confirmed by the complete antagonism exerted by naloxone, which restores initial conditions. Moreover, autoradiographic studies have confirmed that an abundance of opiate receptors exists in the gelatinous substance (II and III lamina of Rexed) of the posterior horn of the spinal cord ([16, 17]). These reports have stimulated the interest of anesthetists in the use of a new route for morphine administration with the aim of achieving a selective spinal analgesia without running the risk of respiratory depression or neurovegetative disorders: the epidural route. This result may be achieved in practice by injecting very low morphine doses (2 mg) epidurally since it avoids the obstacle represented by the blood-brain barrier, which reduces CSF concentrations of morphine to 1/20 of blood levels when the opiate is i.v. administered ([18]).

Cousins *et al.* ([19]) showed that 5 minutes after epidural injection of 100 mg petidine CSF drug levels were higher than concentrations considered analgesic, while blood concentrations were below this level. These and other data suggest that the initial analgesic effect of petidine is due to spinal action; afterwards (40-60 min after injection), analgesia may result from the combination of spinal action (predominant) and central effects, demonstrated by the appearance of sedation.

The biopharmacological characteristics and the consequent anesthetic properties of local anesthetics and opiates explain the simultaneous and sequential use of the two substances via the epidural route.

The theoretical premises, which are confirmed daily in the operating room and later at the patient's bedside, have suggested the best combinations for achieving more encouraging results, even in very elderly patients who often present multiple pathologies and almost always are considered at high anesthesiologic risk. Patients with vulvar neoplasia easily fall into this category.

MATERIAL AND METHODS

From September 1980 to February 1982, all patients with vulvar neopalsia and scheduled for surgical exeresis underwent continuous epidural

anesthesia by administration of local anesthetics and morphine.

Pre-medication was carried out with i.m. injection of 0.5 mg atropine and 50 mg trazodone (Trittico, Angelini). A large arm vein was cannulated and a solution of plasma expander was infused. Every patient was then invited to assume a sitting position, and epidural puncture was performed under absolute asepsis using a 18 G Twohy disposable needle. The epidural space was identified according to Dogliotti [20] and a small Deseret type mandrin-equipped catheter was introduced for a length of about 3 cm in the cranial direction. The needle was slipped out and the catheter held carefully in place with bandages along the patient's back up to the upper margin of the right clavicle. The space selected for epidural puncture was mostly between the 3rd and 4th lumbar vertebra. The median route was preferred, but in the impossibility of passing between the spinous processes, the paramedian route was used. Following aspiration in order to rule out the presence of blood or CSF, a standard dose of 5 ml of anesthetic solution was injected. After 5 minutes, and after excluding the presence of subarachnoid block, another 10 ml of local anesthetic associated to 2 ml morphine (1 mg/ml) were injected.

The local anesthetics used, in different association according to the clinical requirement, consisted of 2% mepivacaine (Carbocaina, Pierrel) and 0.5% bupivacaine (Marcaina, Pierrel). On some occasions, 4-5 ml epinephrine were used (1:200,000).

The morphine solution was prepared from the standard commercial presentation containing 10 mg/ml morphine and 1 mg/ml sodium metabisulphite as preservative. By adding 9 ml of saline solution, a working stock solution was obtained containing 1 mg/ml morphine. A 2 ml aliquot of this solution was administered epidurally before surgery together with the local anesthetic. The working stock solution was stored in the dark for not more than 48 hours, and was also employed for post-surgical pain relief. On specific request by the patient, the paramedic staff administered 2 mg of morphine in a total volume of 6 ml epidurally. No other analgesic, sedative or hypnotic agent was prescribed, and eventual side effects were studied.

RESULTS AND DISCUSSION

Our series consists of 16 patients, ranging in age from 52 to 83 years (mean age: 70.4 ± 8.5 y).

Intraoperatory anesthesiological conditions were considered excellent "ab initio" in 11 cases. This judgement was based on a positive subjective opinion of the patient (calm and completely at ease during surgery), and then on the physician's objective opinion regarding the working conditions. In 4 patients who were particularly anxious during the preoperatory period and mistrustful regarding peripheral anesthesia, it was necessary to complement the local anesthetic-morphine combination with small doses (0.5-1.0 mg) of flunitrazepam (Roipnol, Roche) i.v., which proved sufficient to assure excellent relaxation until the end of surgery. In a single case, as soon as surgery was initiated, it was considered opportune to administer a further dose of local anesthetic (6 ml) and morphine (2 mg). General anesthesia, parenteral administration of analgesic or inhalation of anesthetic gas were not necessary in any case.

During the post-surgical period, 14 patients (87.5%) requested at least one dose of epidural morphine. Specifically, 3 requested a single injection, 6 two injections, and the remaining five asked for three. The latent time necessary for full analgesic action was about 30 minutes.

The duration of analgesia with the first post-surgical dose in the 11 patients who requested more than one application was 16.0 ± 5.2 hrs, the duration of the second post-operatory dose in the 5 patients who asked for a third application was 21.8 ± 4.0 hrs.

During the post-surgical period, none of the patients required sedatives or hypnotics, and no side effects were observed. In a single case, the patient complained of pruritus on the abdomen and legs; this symptomology was relieved with antihistaminic drugs and did not reappear. All the patients stated their satisfaction with the intra-operatory and post-operatory treatment. In particular, two patients who had undergone conventional epidural anesthesia elsewhere for unrelated previous disease reported that they found this method of post-surgical analgesic control qualitatively better.

In no case was a delay in canalization recorded. This should not surprise if one considers that the gastroenteric system, although rich in receptors for opiates especially at the level of Meissner's myenteric plexus, in practice is not involved significantly by the very low blood morphine levels deriving from the very small amounts of morphine administered epidurally.

The merits of epidural administration of morphine are evident both during surgery and especially during the post-surgical period. In fact, during surgery the association of morphine and local anesthetic determines an evident synergistic action in the sense of enhanced surgical anesthesia, and a highly desired complementary effect in the sense of creating a good state of sedation. Still more important is the role played by epidural morphine during the post-surgical period where the qualities of this technique are better expressed. Currently this method appears qualitatively and quantitatively superior to every other type of post-surgical antalgic pharmacotherapy. Nevertheless, there are reports of presumed inefficacy ([22]), and even risk ([23]) following the use of epidural opiates. It should be said, however, that in these cases the clinical studies were not carried out under optimal conditions, both as analgesia was tested after 20′ ([22]), i.e. in the latency phase, and as epidural dosage was similar to that used for i.m. administration ([23]), and therefore excessive. However a rational and meditated use, mindful of hazardous synergisms (for example, epidural morphine and systemic opiates), constitutes a guaranty of efficacy and security. In fact, numerous trials with highly favourable results in the control of both post-operatory ([9, 12, 18, 24]) and cancer pain have been reported ([9]). In patients undergoing heart surgery as well ([25]), the use of intrathecal morphine has proven a precious aid in the control of thoracic pain.

In conclusion, the experience acquired thus far with the use of epidural morphine during the peri-operatory period confirms the efficacy and safety of the method also in elderly patients with neoplasia and multiple pathologies of various etiology.

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