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Long-lasting Epidural Sensory Blockade by n-Butyl-p-Aminobenzoate in the Terminally Ill Intractable Cancer Pain Patient

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An aqueous suspension of n-butyl-p-aminobenzoate (BAB), a highly lipid-soluble congener of benzocaine, was applied epidurally in terminally ill cancer patients with intractable pain. The suspension consisted of 10% BAB and 0.025% of the nonionic surfactant polysorbate 80 in 0.9% sodium chloride. Twelve consecutive patients received epidural BAB because pain was uncontrollable either by palliative radiotherapy or oral or epidural administrations of analgesics. The catheter or injecting needle was positioned at the segmental level of the pain. Repeated epidural injections were administered. In all patients, long-lasting sensory blockade (segmental analgesia) occurred, accompanied by a marked reduction or even absence of pain. In all patients, treatment with epidural opioids, alone or combined with local anesthetics, was no longer necessary. Five of the 12 patients did not require further administration of oral opioids. Motor, bowel, and bladder function were well preserved. In 6 patients, extensive necropsy of the spinal cord and spinal nerves did not reveal pathomorphologic changes. The outer aspect of the dura showed signs of focal necrosis on microscopy, yet its collagen structure and thickness were unchanged. Epidurally, focal infiltrative reactions were seen. The epidural use of an extremely lipid-soluble— hence hydrophobic— local anesthetic, with an exceptionally low *p*Ka (2.3), formulated in suspension of the base, is conceptually innovative and needs further investigation. The authors conclude that the epidural administration of a BAB suspension may be an effective alternative to the neurolytic agents alcohol and phenol and may replace procedures such as cordotomy. Further investigation to determine the safety of BAB in this patient group appears warranted. (Key words: Anesthetics, local: N-Butyl-p-aminobenzoate. Anesthetic techniques: Epidural. Neurotoxicity. Pain: Cancer.)

IN EUROPE and North America about one fifth of the population dies of cancer, and two thirds of these patients suffer from pain at some point during the course of the malignant disease.[1] Although progress in pain treatment has been made in recent years, pain may be severe and difficult to treat.

The discovery of opioid receptors in the spinal cord was first reported in 1973.[2] As a consequence, continuous epidural or intrathecal opioid administration, alone or in combination with dilute solutions of local anesthetics, has enhanced pain management of the patient with intractable cancer pain. However, patient discomfort, catheter-related problems, poor responses, development of tolerance, and logistical problems with home care has tempered the initial enthusiasm.[3,4] Intrathecal or epidural neurolytic blocks with either alcohol or phenol show variable effectiveness and may cause serious side effects, such as neuritis, involvement of major motor nerves, and bowel or bladder dysfunction.[5]

Recently, Shulman *et al.* administered a suspension of the local anesthetic n-butyl-p-aminobenzoate (BAB) epidurally to six dogs.[6] They also administered the BAB suspension to patients with intractable cancer pain. This resulted in sustained pain relief without neurologic deficits in the majority of patients, and Shulman postulated that slow release of BAB from the particles caused the long-lasting effect.[7]

The BAB suspension, prepared as described by Shulman *et al.*,[6] showed separation within seconds of the solid phase from the liquid phase, with part of the BAB floating on the suspending medium. To improve the quality of

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N-Butyl-p-aminobenzoate suspension was prepared by the Department of Clinical Pharmacy, Catharina Hospital, Eindhoven, The Netherlands.

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** Grouls RJE, Ackerman EW, Machielsen EJA, Korsten HHM: N-butyl-p-aminobenzoate: Preparation and quality control of a suspension injection for epidural analgesia. Pharmaceutisch Weekblad Scientific Edition 13:13–17, 1991.

the BAB suspension, Grouls *et al.* developed a new suspension formula,** and we administered this new suspension epidurally to dogs.[8] After repeated injections, this resulted in long-lasting sensory blockade without motor effects. Slight but consistent pathomorphologic changes, especially in dorsal spinal nerve roots and dorsal columns, were found in all dogs treated epidurally with the BAB suspension.

Inducing pathomorphologic changes in nervous tissue is acceptable in patients with cancer-related intractable pain, as long as the treatment is effective and the side effects are minimal. Since the induced pathomorphologic changes in the dog were found mainly in the dorsal spinal nerve roots, and complications did not occur either in dogs or in humans[7] after repeated epidural administrations of BAB, we administered the new BAB suspension in patients with intractable cancer pain that was not adequately relieved by radiotherapy, oral medications, and epidurally administered opioids alone or combined with a local anesthetic. In these selected patients we otherwise would have performed either a cordotomy or would have administered intrathecal or epidural phenol or alcohol.

The present paper describes the technique and the results of the epidural administration of the new BAB suspension in the first 12 consecutive patients with intractable cancer pain. In 6 of them pathomorphologic findings in the spinal cord and associated structures are also described.

We also present information considered crucial to evaluate the efficacy of a blockade in intractable cancer pain[9]: 1) detailed information of analgesics and dosages before and after blockade; 2) a qualitative and quantitative assessment of pain before and after blockade; 3) duration of pain relief and whether pain relief lasted until death; 4) at what point during the course of the disease blockade with BAB was used; and 5) adverse effects.

Materials and Methods

A sterile 10% BAB suspension was prepared by suspending 3 g BAB (OPG, Utrecht, The Netherlands) in 30 ml sodium chloride 0.9% containing 0.025% polysorbate 80 (OPG, Utrecht, The Netherlands), as described in detail by Grouls *et al.*** The median particle size was 15 μm; the range of the particle size varied from 1 to 100 μm (fig. 1). BAB was shown to be extremely lipid-soluble: the partition coefficient of BAB in octanol/phosphate buffer (pH = 7.4) is 1,028 ± 51 at room temperature, whereas the partition coefficient of bupivacaine in octanol/phosphate buffer (pH = 7.4) is only 62 ± 3. BAB has a very low pKa (2.3) and a very low solubility in water (1 g BAB in 7 l water).[10]

Patients

Epidural administration of BAB in 12 patients with advanced cancer and intractable pain was approved by the Hospital Ethics Committee (table 1). Informed consent was obtained from all patients after fully explaining the nature of the experimental treatment and possible consequences of the epidural administration of BAB. It was emphasized—orally and in writing—that experience with

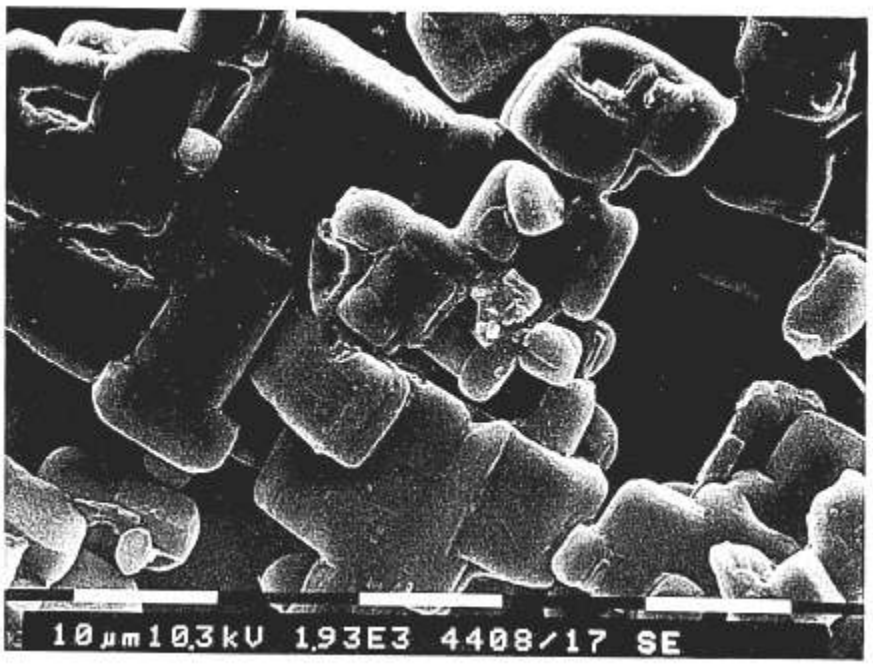

FIG. 1. Scanning electron microscopic (SEM) picture of BAB particles in suspension, after application of a gold layer of 7 nm (electron beam energy 10.3 kV, magnification 1930, Philips SEM). A black or white dash on the dashed black-and-white line indicates a distance of 10 μm.

TABLE 1. Patient Data

Patient Number and Sex	Age (yr)	Cancer Site	Surgery	pTNM (Stage) at Time of Diagnosis	rTNM (Stage) at Time of BAB Administration	Days Between Diagnosis and Therapy with BAB
1 F	69	Vulva	Vulvectomy	T1N1M0 (I)	T1N1M1 (IV)	360
2 F	69	Cervix	None	T2bNxM0 (IIb)	T3NxM1 (IVb)	890
3 M	75	Rectum	Rectum-amp.	T3N0M0 (II; B[1])	T4N0M0 (II; B[1])	530
4 M	63	Bladder	Cystectomy	T2NxM0 (II)	T4N0M0 (IV)	220
5 M	71	Rectum	Rectum-amp.	T2N1M0 (III; C[1])	T4N1M1 (IV; D)	800
6 M	44	Lung	Pneumonectomy	T2N1M0 (II)	T4N3M1 (IIIB)	120
7 M	61	Bladder	Cystectomy	T4NxMx (IV)	T4NxMx (IV)	210
8 F	29	Cervix	None	T2NxM0 (IIb)	T4NxM0 (IVa)	270
9 F	55	Mamma	None	T4N2M1 (IV)	T4N2M1 (IV)	1297
10 M	72	Lung	Thoracotomy	T4N0M0 (IIIb)	T4N2M1 (IV)	480
11 M	55	Unknown primary tumor	None	TxNxM1	T2N3M1 (IV) (autopsy)	87
12 F	60	Rectum	Hemicolectomy	T3N1M0 (III; C[1])	T4N3M1 (IV; D)	810

Tumor–node–metastasis (TNM) classification according to the International Union Against Cancer general rules. The prefix "p" reflects data of the tumor acquired from surgery and pathomorphologic examination; recurrent tumor manifestations are indicated by the prefix "r" (*e.g.*, in patient 6, at surgery a lung carcinoma was diagnosed invading the visceral pleura [pT2], associated with ipsilateral hilar lymph node involvement [pN1] without metastasis [pM0]. This tumor recurred after pneumonectomy with invasion of a vertebral body [rT4] with metastasis to a supraclavicular lymph node [rN3] and skin metastasis [rM1]).

BAB = n-butyl-p-aminobenzoate.

this new suspension was limited and that, although we did our utmost to prevent serious complications such as paralysis or interference with micturition and defecation, these complications could occur. Before considering the epidural administration of BAB, all but one patient were treated with oral opioids and analgesics in combination with epidural morphine alone or sufentanil in combination with bupivacaine, either as single injection or by continuous infusion (table 2). Only when this treatment failed and life expectancy was believed to be limited to several months, did we propose that the patients receive BAB epidurally. One patient refused a long-term epidural catheter for opioid administration and had palliative radiotherapy only in order to reduce her pain. Despite this treatment, the tumor mass as well as the pain increased. This patient also received BAB epidurally after informed consent, since she was in great pain and her life expectancy was considered to be very limited.

Seven men and five women were studied (median age 62 yr; range 29–75 yr). The median time between diagnosis of cancer and treatment with BAB was 420 days (range 87–1,297 days). The median tumor–node–metastasis (TNM) classification (a system that uses tumor size, node involvement, and distant metastases) and stage (a classification that predicts the general clinical course) increased from pT2N1M0/stage II at the time of diagnosis of the cancer to rT4N2M1/stage IV at the time of treatment for pain with BAB (table 1).

Pain was experienced at different sites of the body, frequently interfering with daily activities and with sleep. Apart from a variety of oral analgesics, sedatives, tricyclic antidepressants, and corticosteroids, the patients were having a median daily epidural dose of 21 mg morphine (range 0–500 mg) for a median duration of 21 days (range 0–169 days) (table 2). All patients had lost at least 10% of their body weight in the previous 12 months.

TABLE 2. Pain Description and Epidural Medication Prior to BAB Treatment

Patient Number	Site(s) of Pain	Epidural Opioids Daily	Days on Epidrual Opioids	Description of Pain
1	Lower abdomen and leg	6 × 3 mg morphine	97	Sharp and pressing, unable to move leg
2	Lower abdomen and leg	None	—	Sharp spasms, difficulty with walking
3	Perineal pain	6 × 3 mg morphine	30	Glowing needles and pins, could not sit
4	Lower abdomen, leg, and perineum	8 × 3 mg morphine	62	Dull pressing pain
5*	Lower abdomen and leg	6 × 3 mg morphine	4	Spasms and cramps, unable to walk
6*	Hemithorax	6 × 10 mg morphine	92	Sharp spasmatic pain
7*	Lower abdomen and perineum	6 × 3 mg morphine	4	Dull pressing pain
8	Lower abdomen, hip, leg, and foot	40 ml bupivacaine 0.2% + 1.2 mg sufentanil	6	Pressing pain and tingling foot
9	Sacrum	40 ml bupivacaine 0.2% + 1.2 mg sufentanil	14	Burning pain, unable to sit
10	Hip, leg, and foot	3 × 3 mg morphine	28	Sharp pain and numb foot
11	Hemithorax	30 mg morphine	14	Sharp pain
12*	Lower abdomen and perineum	500 mg morphine	169	Burning and pressing pain

* Patient referred from another hospital.

Since one of the metabolites of BAB is p-aminobenzoic acid (known to be allergenic), the patients were specifically asked whether they were allergic to local anesthetics, drugs, food, or sunburn lotions. In none of the patients was this the case.

Treatment with epidural BAB (usually applied *via* a catheter; for details see appendix) was ended when adequate pain relief had been obtained or when no further improvement or increase in sensory blockade after repeated injections occurred. The highest cumulative volume of BAB given epidurally in this study was 130 ml (13 g BAB). After removal of the catheters the tips were examined for bacterial contamination.

Functional Evaluation of BAB-injected Patients

The dermatomal level of analgesia was assessed by loss of pinprick and cold discrimination using the dermatomal chart described by Bromage.[11] After each BAB administration the patients were monitored in the recovery room for at least 2 h. The most craniad and caudad extension of the area of sensory loss was determined by asking the patient to compare a pinprick and cold applied with an ether gauze to an unanesthetized area. Motor blockade of the legs and the abdominal wall muscles was tested by the criteria described by Bromage[11] and Van Zundert *et al.*[12]

After discharge, patients were visited and assessed at home at regular intervals by one of the authors (H.H.M.K.) and the family physician. The family physicians of two patients living at remote distances from the hospital tested the level of analgesia and reported the intensity of pain and changes in opioid prescription until death.

Pathomorphologic Evaluation in Six Patients

After permission from the families, necropsy was performed in six patients. The spinal cord, spinal nerves, and associated structures including spinal ganglions were removed *via* anterior laminectomy. Saw cuts with an electric vibrating saw were made in front of the exit foramina of the spinal nerves. These cuts expose the anterior surface of the dura as well as nerve roots and spinal ganglions. This approach entails less risk of damage to the cord and leaves the dorsal subcompartment of the epidural space intact.[13] The spinal cord with nerve roots and spinal ganglions were removed and fixed in 4% buffered formaldehyde solution for gross and light microscopic examination. Cross sections of the spinal cord and cross sections and longitudinal sections of spinal nerves and ganglions were embedded in paraffin, cut into 5-μm sections, and stained with hematoxylin and eosin, Sudan black, and Klüwer-Barrera.

Results

A total of 71 epidural BAB administrations were given to the 12 patients (median 5, range 2–12 administrations per patient). A median volume of 10 ml (range 4–17 ml) per injection and a median total volume of 56 ml of BAB (range 4–129 ml) was administered epidurally either *via* the catheter or as single injections at multiple segmental levels. The median duration of treatment was 3 days (range 2–14 days) (table 3).

In all patients, epidural opioid dosages could be reduced after the first BAB administration and were stopped at the end of the treatment with BAB. Five of the 12 patients did not require oral opioids until death (table 3). Two patients, who had been confined to bed because of the pain, could sit and walk again without great difficulty.

All injections *via* the catheter were accomplished without complications. In patient 3 (table 1), injection of 1 ml BAB after a test dose of 1% lidocaine with epinephrine 1:100,000 *via* the Tuohy needle while attempting a caudal block was followed immediately by severe nausea and vomiting, accompanied by tonic and clonic cramps. The patient did not lose consciousness. Prompt treatment with 100% oxygen by mask and 10 mg diazepam intravenously resulted in complete recovery within 4 min.

Functional Evaluation of BAB-injected Patients

None of the patients showed paralysis after the epidural administration of 1% lidocaine with epinephrine 1:100,000 and BAB. Some patients reported a tingling heavy sensation in the feet or legs for approximately 1 h but could easily move their feet and legs (0% block on Bromage's[11] test). The muscle power of the rectus abdominal muscle, assessed before and 1 h after BAB administrations, was also not changed. Blood pressure decreased in all patients after lidocaine 1% with epinephrine and BAB but was managed without difficulty by infusion of crystalloid.

In all patients analgesia was present in one or more segmental levels 24 h after the first BAB administration. Since the analgesia was not extensive and pain relief was insufficient, all patients required more than one epidural administration of BAB. Repeated injections resulted in extension of the analgesic dermatomal segments in all patients (table 3 and fig. 2). Sensory blockade lasted until death in 10 of the 12 patients (median duration 29 days; range 6–133 days). A repeated series of epidural BAB administrations was necessary in 2 patients. Patient 2 had a second block after 138 days because the pain had re-

TABLE 3. BAB Treatment and Resulting Analgesia

Patient	Tip of Epidural Catheter (Site of Puncture)	Administrations of BAB (n time/days)	Volume of BAB (ml)	Analgesia (Pin Prick/Ether Gauzes)	Subjective Assessment of Pain after BAB	Daily Opioid Administration after BAB	Duration of Analgesia (days)
1	T12 (L3–L4)	3/3	20	T11–L3	Complete relief	No opioids	6 until death*
2[a]	T12 (L3–L4)	3/3	20	T4–L3	Complete relief	No opioids	138†
2[b]	s L2–L3–L4	5/12	64	T4–L3	Complete relief	No opioids	190
3, nec.	L4 (L5–S1)	2/2	19	T10–T11	Partial relief, perineal pain	2 × 30 mg MS oral‡	
3	S1–S2 (caudal)	2/2	4‡	T10–T11	Partial relief	2 × 30 mg MS oral	28 until death*
4, nec.	T12 (L3–L4) + 3 × s L5–S1	5/7	62	T6–L5	Good relief	Sporadic, 10 MS oral	20 until death§
5, nec.	T11 (L4–L5), + s L2–L3	6/6	48	T4–L5 (L2–L3 patchy)	Complete relief	No opioids	71 until death*
6	T6 (T12–L1) + s T10–T11	4/4	26	T2–L2	Complete relief	No opioids	65 until death§
7	L3–L4 (L5–S1)	4/3	60	T10–S2 (L2–L3 patchy)	Good relief	2 × 10 mg MS oral	36 until death*
8[a]	T12 (L4–L5)	12/14	129	T10–L2	Fair relief, tingling foot	2 × 30 mg MS oral	
8[b]	L5 (caudal)	5/3	80	T7–S2	Fair relief	2 × 30 mg MS oral	133 until death*
9	L4–L5 (caudal)	3/2	21	T8–S4	Complete relief	No opioids	50 until death*
10, nec.	L3–L4 (caudal) + s L1–L2	5/2	57	T8–S1	Good relief	2 × 10 MS oral	36 until death*
11, nec.	T6 (T10)	6/5	56	T4–T8	Fair relief	4 × 60 MS oral	16 until death*
12, nec.	L5 (caudal) + s L1–L2	6/11	105	S3–T11	Partial relief	40 mg morphine iv	29 until death§

a and b = First and second series, respectively, of epidural BAB administrations in the same patient; nec = necropsy; s = single injection; MS = MS-Contin®.

* Died at home.

† Sensory blockade wore off and pain reoccurred.

‡ Pain on injection of BAB; patient refused further treatment.

§ Died in hospital.

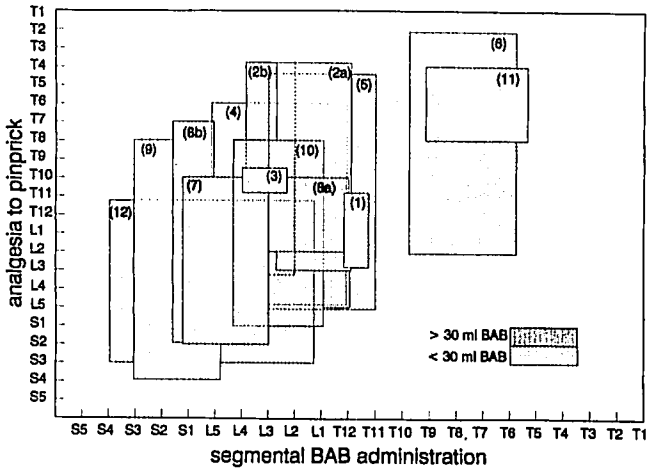

FIG. 2. Analgesia to pinprick 48 h after the last BAB administration. The width of the bars on the x-axis are due to injections at multiple segmental levels. The numbers in brackets refer to patients.

turned. Analgesia to pinprick and cold had completely resolved. This repeated block required a much larger volume of BAB, and the resulting sensory blockade lasted for approximately 6 months (table 3). In this case a third block was not necessary, because pain did not return after cessation of the sensory block. In the other patient (patient 8), a new series of epidural BAB was administered because pain in the left leg and foot was now predominant, and the initial treatment had been for abdominal pain (table 3). In two patients (patients 5 and 6), we observed that 2 months after the last BAB administration, analgesia was less profound, more patchy, and less extensive than it had been. Blockade was not repeated, since these patients had no pain.

As expected, the levels of sensory blockade corresponded with the segmental levels at which BAB was administered (fig. 2). This segmental sensory effect was so pronounced that BAB given *via* a catheter lying in one dorsolateral subcompartment of the epidural space, as visualized by computed tomography scan, induced long-lasting sensory blockade only on the ipsilateral side.

To achieve the desired level of sensory blockade a large variation of BAB volumes was necessary. In some patients the segmental level of sensory blockade increased for 2 or 3 days after the last BAB administration, even after a relatively low volume (*e.g.*, patient 2[a], table 3). Repeated large volumes in other patients however, did not increase the extent of sensory blockade (*e.g.*, patient 8[a], table 3).

Side effects included drowsiness (n = 2), nausea (n = 2), urinary retention requiring bladder catheterization for 2 days (n = 1), and pain in the back 2–4 days after the catheter placement (n = 6). One patient reported extreme pain in the back on injection of lidocaine or BAB. This pain made it impossible to administer an adequate volume of BAB (table 3; patient 3).

None of the patients complained of the resulting analgesia. All but two patients noticed analgesia only when tested by themselves or by the doctor. Two patients reported an unusual sensation: patient 9 experienced the sensation of sitting on very small stones, and patient 10 noticed numbness in a foot when walking. None of the patients regretted his or her consent to take part in this study.

All but one epidural catheter were contaminated with a variety of microorganisms. One patient (patient 3) was treated with antibiotics dictated by the resistance pattern of the isolated *Escherichia coli.* Contrary to the other patients, the skin of this patient showed signs of exit site inflammation, and *E. coli* was cultured.

Eight of the 9 discharged patients who died, died at home. This is all the more remarkable because all 12 of the patients had been hospitalized for management of intractable cancer pain. The one patient who was readmitted because of severe dyspnea died 2 days later in the hospital (table 3).

Pathomorphologic Evaluation in Six Patients

As expected, routine necropsy disclosed extensive tumor growth and metastatic processes. When the spinal canal was opened, tumor growth was obvious in the dura of one patient (patient 5); in another patient (patient 3) a localized epidural abscess was found in the lumbosacral region. In all patients, small aggregates of BAB were found in the dorsal subcompartment of the epidural space (fig. 3). Apart from these findings, the dura, spinal nerve roots, spinal ganglions, and the spinal cord did not reveal any abnormality on macroscopic examination.

On microscopic examination, no lesions were found in the spinal nerve roots and spinal cord. The spinal ganglions revealed no abnormalities, with one exception; in this patient, some of the spinal ganglions showed signs of atrophy and degeneration. In all patients, the outer one third to one half of the thickness of the dura showed signs of focal necrosis. The architecture of the collagen fibers and the thickness of the dura were not changed (fig. 4). The epidural fat showed signs of necrosis and focal inflammatory infiltration. Furthermore, multinucleated foreign-body giant cells and other histiocytic cells were seen. The foreign-body giant cells contained needle-shaped clefts and crystalline material in the cytoplasm. Neither vasculitis nor eosinophilic granulocytes were seen.

Discussion

This study confirms long-lasting pain relief of as long as 6 months in cancer pain patients after repeated epidural

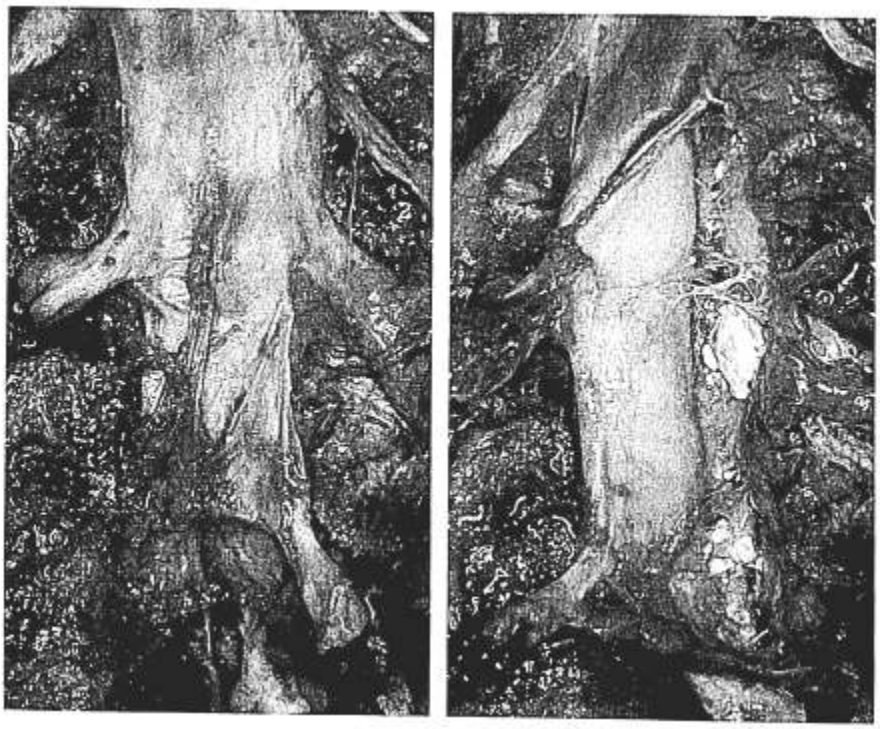

FIG. 3. Patient 10. Dural sac, spinal nerve roots, and spinal ganglions seen from in front, after removal of the vertebral bodies (*left*). After lateral traction of spinal ganglions, nerve roots, and dural sac to the right, the dorsal epidural subcompartiment is exposed, containing BAB lying along the nerve roots L4 and L5 (*right*). BAB (57 ml) was administered 36 days before the patient's death.

administrations of BAB, in agreement with the finding of Shulman.†† Apart from a marked reduction in pain and opioid use, long-lasting sensory blockade to pinprick and cold discrimination without any evidence of motor blockade was established for as long as 6 months. Long-lasting sensory blockade without motor blockade is consistent with our previous results with epidural BAB in dogs, in which a significant increase in stimulation threshold to electric current without concurrent motor blockade was demonstrated for days after repeated epidural BAB administration.[8] These observations do not agree with those of Shulman *et al.* in dogs and in humans, since they reported short-lived sensory blockade for 3–4 h in dogs[6] and for 1 h or less in humans[7] after epidural BAB administration.

This difference in clinical effect is difficult to understand because in both studies the basic chemical substance of BAB (the base form) and not its picrate salt was used to make the 10% BAB suspension.‡‡ This probably rules out a chemical difference in the substance used.

However, there are four distinct differences between Shulman *et al.*'s[6] and our method, as follows. 1) Shulman used polyethylene glycol 3350, a suspending agent, whereas we used the nonionic surfactant polysorbate 80 to make the suspension. 2) The size of the BAB particles in suspension was different: we obtained a median particle size of 15 μm (fig. 1), whereas Shulman reported a particle size of 40 μm.[7] 3) Our protocol of epidural BAB administrations was different. We administered relatively low volumes (7–17 ml) of BAB on consecutive days, whereas Shulman administered a relatively large volume (25–40 ml), which was repeated if necessary. 4) In our study every epidural BAB administration was preceded by administration of 10 ml 1% lidocaine with epinephrine 1:100,000.

We did not find neurolytic changes in the spinal cord and spinal nerve roots after repeated epidural BAB injections in humans, which is different from our finding in dogs.[8] The epidural histiocytic reaction may be a natural response of the body to the remaining undissolved BAB particles. These findings are in agreement with those of Shulman *et al.* in humans.[6]

The degeneration seen in spinal ganglions of one patient was probably not related to the epidural BAB administration, because it was seen in only one of our patients treated with BAB. Similar degeneration is occasionally seen at autopsy in patients not treated with BAB.§§

The focal necrosis of the outer dura layer, present at the levels of BAB administration, was not anticipated. Shulman *et al.*[6] did not report such changes, and we did not observe dural changes in dogs treated with epidural BAB.[8] It is not yet known when these changes first occur and if they resolve. This focal necrosis may originate from

†† Shulman M: Epidural butamben for the treatment of metastatic cancer pain. 9th World Congress of Anesthesiologists, Washington, D.C., May 1988.

‡‡ Shulman M: Personal communication. August 1990.

§§ Van Ketel BA: Die Menschlichen Spinalganglien. Zur Pathologie der Spinalganglien (thesis). Utrecht, The Netherlands, 1979.

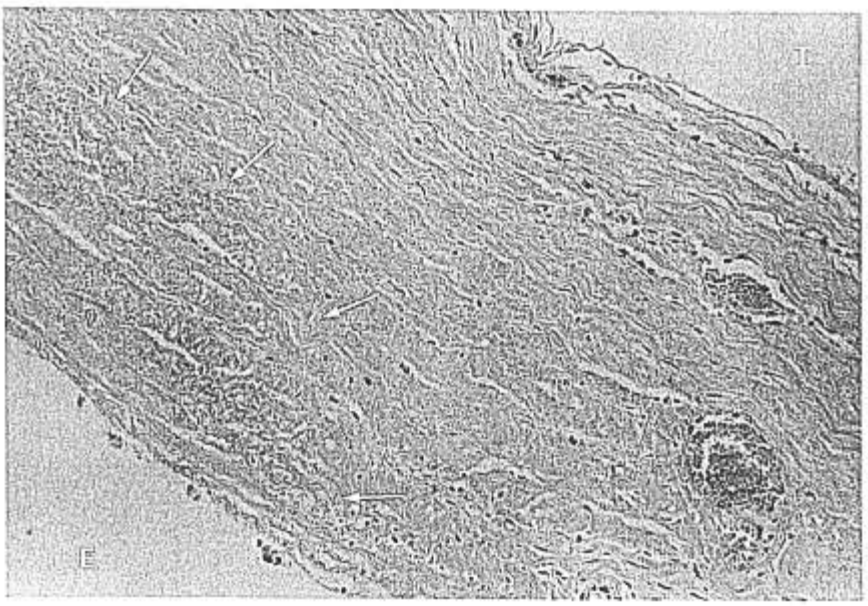

FIG. 4. Patient 11. Section of dura at T6 (hematoxylin in eosin, ×100). Note focal cell necrosis and "nuclear dust" at the outer aspect of the dura (*arrows*). E = epidural; I = intrathecal.

causes other than the administered BAB. Long-term epidural administration of opioids and local anesthetic solutions *via* epidural catheters also lead to deformation of the dura in rats, as demonstrated by Durant and Yaksh.[14] All our autopsied patients had previously received long-term treatment with epidural opioids *via* epidural catheters.

The pathomorphologic changes in the dura may also originate from the administered BAB. It is possible that high concentrations of BAB accumulate in the outer layer of the dura, causing cell necrosis. Shulman *et al.* reported that the intrathecal administration of a 10% BAB suspension in dogs caused adhesive arachnoiditis and thickened and fibrotic dura adherent to the leptomeninges of the cord and spinal nerves, without any evidence of nervous tissue damage.[6] This observation is at variance with the observations after intrathecal phenol in humans, which causes posterior and anterior nerve root damage and demyelination as well as arachnoiditis.[15] The cause and significance of the pathomorphologic changes in the dura in our patients is unclear. It may be clinically insignificant since the structural function of the dura was evidently unaffected.

The epidural abscess in patient 3 originated almost certainly from the epidural catheter used for long-term treatment with opioids, because the catheter was dislodged and the exit site on the skin showed signs of infection. Injection of lidocaine or BAB was virtually impossible because of pain during injection. Therefore, we assume in retrospect that the abscess already existed. Du Pen *et al.*[16] concluded that the use of long-term epidural catheterization is associated with a definable epidural infection rate.

Although a catheter-technique is not necessary to administer BAB epidurally, we used short-term epidural catheterization both for safety and for convenience. The exact position of the tip of the catheter was visualized by fluoroscopy using contrast medium, so that intravascular or intrathecal positions could be ruled out. Another advantage of a catheter is that repositioning, administration of the test dose, and the slow administration of BAB (1 ml/min) can be done with ease and minimal discomfort for the patient. It is noteworthy that a single injection of BAB *via* a Tuohy needle caused tonic and clonic cramps in patient 3, most likely because of intravascular injection of a small dose of BAB.

The most interesting observation in this study is the long-lasting sensory blockade without any evidence of motor blockade. Recently, Fink suggested a novel anatomic basis for the occurrence of differential blockade.[17] He hypothesized that differential epidural block may be explained as follows: conduction can leap two consecutive blocked nodes but not three or more. A local anesthetic administered epidurally bathes only a few millimeters of segmental nerves epidurally. Therefore, three-node block will be rare in large, long-internode fibers but is likely to occur in small short-internode fibers. Thus, Aδ sensory fibers are easily blocked, whereas Aα motor fibers are not expected to be blocked epidurally. Fink concluded with a remark made by an anonymous peer reviewer: "The true test of a useful hypothesis is its ability to predict results of future experiments."

We postulate that our results can indeed be predicted by Fink's[17] hypothesis. BAB has such a low aqueous solubility that substantial diffusion to the CSF is not anticipated. This means that the epidural compartment–based differential blockade is not nullified by diffusion of an-

esthetic through the dural root cuff or dural sac to the spinal nerves intradurally (the latter being probably the essential site of blockade after epidural administration of *solutions* of local anesthetics[18]). Therefore, BAB is probably confined to the epidural space, where it can block only short-internode pain fibers. Raymond *et al.*[19] stated that "because nociceptors are coupled to smaller axons than those studied here, the possibility of producing strongly differential local anesthetic block for pain by restricting the exposure length, cannot be ruled out." Limiting the length of nerves exposed to local anesthetics may be the basic principle involved here and can be applied on both Aδ and C pain fibers in order to explain the strongly differential blockade seen after epidural BAB administration.

The concept of restricting the exposure length of nerves in order to produce a strongly differential local anesthetic block is promising, since it seems to allow the induction of long-lasting analgesia with minimal side effects by long-lasting exposure of nervous tissue epidurally to local anesthetics, which neither create an effective concentration in the CSF nor are quickly distributed to the systemic circulation. A local anesthetic with physicochemical properties like BAB (*e.g.*, a very low *p*Ka and a very low solubility in water), administered epidurally in a suitable form (*e.g.*, a suspension) can indeed produce a long-lasting sensory effect, as demonstrated by Shulman[7] in humans and our group in dogs[8] and in humans. The fact that a suspension has a high shear resistance, which supposedly limits its ventral spread, is an additional safety factor (fig. 3).

The paper by Fink[17] was accompanied by an editorial, in which Raymond and Strichartz stated that at present the field is at a cusp.[20] Apart from size-based and susceptibility distinctions between fibers, they described other distinctions that may be essential in explaining differential blockade: variation in the incremental changes in ion concentration following impulses; relative densities of Na^+ and K^+ channels; metabolic activity (ion pumps) required to restore the ionic gradients; and differences in binding kinetics of the ion channels in the different fibers.

There are additional possible explanations for our results. The spinal cord may play a role and can theoretically act as a sponge, absorbing large quantities of BAB, despite the low concentration of BAB in the surrounding CSF. This phenomenon has been demonstrated by Boersma *et al.*¶¶ for sufentanil, which is also a very lipophilic drug.

Currently, we can only speculate on the intrathecal, epidural, and systemic distribution of BAB after its epidural administration as a suspension.[21] The test dose, containing 1% lidocaine with epinephrine 1:100,000 probably also influences the local and systemic distribution of BAB. Whether this influences the clinical result also has to be determined. Autoradiography and concentration–time profiles of BAB in CSF and plasma may answer some of these questions. Furthermore, neurophysiologic studies before and after epidural BAB administration are indicated in animals and humans to measure changes in sensory modalities, which are processed centrally along a diversity of pathways at different segmental levels.

The large variation in BAB dosages required to induce pain relief is difficult to explain. Factors such as epidural fat content, epidural compliance, the position of the patient immediately after the block, and leakage of BAB *via* the intervertebral foramen may influence the epidural deposition of the BAB suspension. The nerves in the dorsal epidural subcompartment presumably are randomly bathed by the BAB suspension. This also may explain the large variation in the amount of BAB necessary to produce analgesia. A technique that makes it possible to administer BAB in the vicinity of the appropriate spinal nerve roots can theoretically improve the results. Paravertebral blockade may be a suitable alternative to conduct the BAB suspension to the segmental nerve roots,[22] yielding a more predictable result.

The epidural depot of BAB may produce long-lasting analgesia by the slow release of BAB, resulting in long-lasting high BAB concentrations in the lipids surrounding the axons of the spinal nerves. Although we did not find any evidence for neurotoxicity of BAB in humans, neurotoxicity of BAB remains a major concern. Kalichman *et al.* specifically stated that both amide- and ester-linked local anesthetics produce a comparable spectrum of nerve injury and that this injury has general clinical relevance.[23]

In conclusion, we have demonstrated that the epidural administration of a 10% BAB suspension in humans induce long-lasting sensory blockade without motor blockade. The intractable cancer pain that was not amenable to radiotherapy or oral and epidural opioids alone or in combination with local anesthetics was alleviated in the first 12 consecutive patients after repeated administrations of BAB. Neurotoxicity of BAB could not be demonstrated, although the outer aspect of the dura mater showed signs of focal necrosis. The long-lasting differential block resulting from the epidural administration of BAB seems to endorse theories that are based on the length of exposure of nerves to local anesthetics.[17,19] More research is necessary to define the distribution of BAB after its epidural application and to characterize toxicity.

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¶¶ Boersma FP, Meert TF, ten Kate A, Pieters W, Noorduin H: Cancer pain control by epidural sufentanil. Eur J Pain 11:76–80, 1990.

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Appendix

During the study, we gradually improved our technique. Since conventionally used epidural catheters were easily blocked by the BAB particles once the catheter was *in situ*, we changed from the midline to the paramedian epidural approach. It has been demonstrated that a catheter introduced with the paramedian approach is easily passed in a cephalad direction with a cranial angle of 125–135°.[24] We inferred that the acute angle on entering the epidural space using the midline approach (commonly 90–100°) facilitated the obstruction of the catheter by BAB particles. Furthermore, instead of using the usual epidural catheters, polyurethane intravascular catheters (14-G, 30-cm Vialon® catheters) were placed in the epidural space, *via* a modified Seldinger technique.

After local infiltration with 2% lidocaine, the epidural space was identified with a 16-G Tuohy needle using the loss-of-resistance technique with normal saline. The patients were usually lying prone on the operating table with a cushion under the abdomen or pelvis. Once the epidural space was entered, a straight Teflon-coated guide wire with a soft tip and a movable core (Emerald®, Cordis®, 150 cm in length and 0.035 in inches diameter) was inserted. The guide wire was advanced at least three or four segmental levels higher than the desired place of the catheter tip in the middle of the dorsal subcompartment of the epidural space. While advancing the guide-wire, its position was continuously visualized in two directions with an image-intensifier (Philips BV-25). The movable core made it possible to a certain extent to steer the guide wire.

Once the guide wire was satisfactorily positioned in the middle of the dorsal epidural subcompartment, the Tuohy needle was removed and the path for the catheter was dilated using vessel dilatators (Cordis®, 6–8-Fr). The tip of the polyurethane catheter was positioned epidurally over the guide wire at the segmental level corresponding with the site of the maximal pain. In three patients we modified our technique as follows: we approached the hiatus sacralis laterally through the gluteus muscle in order to prevent contamination from the intergluteal fold; the sacral canal and higher epidural space—once identified—were filled with 20 ml normal saline, and the guide wire and catheter were advanced as described above. Once the catheter was in place, we injected 3–4 ml Iopamidol (400 mg/ml) to confirm its correct placement in the dorsal epidural subcompartment. In addition to this, we made computed tomography scans in the first five patients to better localize the catheter tip and the spread of the contrast medium.

All patients had an intravenous catheter. Monitoring during and after the epidural administration of a test dose of lidocaine with epinephrine 1:100,000 or BAB included electrocardiography, automatic blood pressure measurement, and pulse oximetry. The patients were lying on the side to be blocked, and after negative aspiration, 10 ml 1% lidocaine with epinephrine 1:100,000 was given in two fractions with a 5-min interval between fractions. The second fraction was given when the intravascular or intrathecal position of the catheter had been ruled out. After 30 min, epidural BAB was given at a rate of 1 ml/min. Patients were continuously monitored and asked whether they noticed something unusual (*e.g.*, dizziness or nausea) during injection. They were also repeatedly asked to move their legs and toes. The volume was gradually increased, starting with 7 ml during the first injection, but not exceeding 17 ml per injection. All patients had bed rest for at least 6 h after the injection.

Repeated injections of BAB were given in all patients, at first once per day, but later during the study twice per day. Frequently, the catheter was pulled downward in the epidural space in order to administer BAB at lower segmental levels. Repositioning of the catheter was done under x-ray control. If it was not possible to pull the catheter back to the desired segmental level, or if the catheter was removed, single injections of epidural BAB were given at the appropriate segmental level, always preceded by a test dose of lidocaine and epinephrine 1:100,000.

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