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Long-lasting Epidural Sensory Blockade by n-Butyl p-Aminobenzoate in the Dog: Neurotoxic or Local Anesthetic Effect?

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An aqueous suspension of n-butyl p-aminobenzoate (BAB), a highly lipid-soluble congener of benzocaine, was applied epidurally and around ulnar nerves in dogs. The suspension consisted of 10% BAB and 0.025% polysorbate in 0.9% NaCl. Sensory effects were tested by electrical stimulation. Three epidural injections were given, and the dogs were killed after 21 days. The increase in stimulation threshold was comparable to the effect of lidocaine in a concentration between 0.5% and 1%. Increased sensory threshold lasted for days, whereas no long-lasting motor effects were observed. Pathomorphologic changes were found primarily in the dorsal spinal nerve roots, although slight changes were also found in the ventral spinal roots. White matter degeneration was found only in the lumbar dorsal columns. This result suggested Wallerian degeneration in the dorsal spinal nerves and was at variance with recently published data on epidural BAB. No changes were observed in the ulnar nerves. The authors demonstrated that the pathomorphologic changes were induced by the BAB suspension and not by the suspending additive polysorbate 80. It was postulated that the suspension of BAB, which contains particles of a median size of 15 μm, was mainly confined to the dorsal epidural space where neurolytic changes in axons of the dorsal spinal nerve roots and dorsal columns are induced. This may explain the long-lasting sensory effects seen in intractable cancer pain patients after epidural BAB administration. More research is necessary to define the distribution of BAB in nervous tissue after its epidural administration and to better characterize toxicity, neurolytic effects, and regeneration of nervous tissue after BAB administrations. (Key words: Anesthetics, local: n-butyl p-aminobenzoate. Anesthetic techniques: epidural. Pain: cancer.)

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TREATMENT OF INTRACTABLE cancer pain remains a major problem, although progress has been made in recent years. Local anesthetics, usually bupivacaine alone or in combination with opioids, have been infused epidurally or intrathecally over a long period. These techniques have limitations, such as discomfort to the patient, catheter-related problems, and the development of tolerance to the drugs used.[1] Intrathecal or epidural neurolytic blocks with either alcohol or phenol also are used but are not always effective and may cause serious side-effects, such as neuritis, involvement of major motor nerves, and bowel or bladder dysfunction.[2]

Epidural administration of a non-neurolytic, non-opioid local anesthetic, administered as a slow release preparation, may have advantages over opioids or neurolytic agents in the management of intractable cancer pain. A suspension of n-butyl p-aminobenzoate (BAB), an "old" local anesthetic that is practically insoluble in water, may fulfill this requirement.

In 1947, Kenny reported the successful use of "proctocaine," which included (in part) BAB and benzyl alcohol, in 17 patients with intractable cancer pain of the pelvis. The duration of pain relief after one to three epidural injections varied from 3 weeks to 4 months, and in all but four patients, pain relief was sustained until death.[3] It was shown, however, that benzyl alcohol caused long-term sensory effects.[4]

Recently, Shulman administered a BAB suspension without neurolytic agents epidurally in six dogs. There were no demonstrable pathomorphologic changes in the spinal cord, spinal nerves, or associated structures.* Subsequently, he administrated the BAB suspension in patients with intractable cancer pain. This resulted in sustained pain relief without neurologic deficits in the majority of patients.† In 20 of 25 patients, pain relief was considered to be successful, and in 12 patients, pain relief was sustained up until the time of death. The five patients

* Shulman M, Joseph NJ, Haller CA: Local effects of epidural and subarachnoid injections of butyl-amino-benzoate suspension (abstract). Regional Anesthesia 12:23–24, 1987.

† Shulman M: Treatment of cancer pain with epidural butyl-amino-benzoate suspension. Regional Anesthesia 12:1–4, 1987

who were considered to be therapeutic failures had received only a single epidural injection with BAB‡.

The BAB suspension, prepared as described by Shulman, showed rapid separation between the solid and liquid phase (seconds), with part of the BAB floating on the suspending medium. To improve the quality of the BAB suspension, we developed a new suspension formula (see Methods).

In the current study, this new BAB suspension was administered epidurally and perineurally (ulnar nerve) in dogs 1) to determine the clinical effects of epidural administrations of BAB, 2) to compare the effects of epidural BAB with the effects of various concentrations of lidocaine HCl, and 3) to determine whether the BAB suspension induced pathomorphologic changes in the central nervous system (CNS) and the ulnar nerves.

Methods

BAB Suspension

A sterile, 10% BAB suspension was prepared by suspending 3 g n-butyl p-aminobenzoate (OPG, Utrecht, The Netherlands) in 30 ml of 0.9% NaCl containing 0.025% polysorbate 80 (OPG, Utrecht, The Netherlands).§ After sterilization (20 min at 121° C, cycle without cooling), the liquid mixture was cooled to room temperature during vigorous mechanical shaking (Marius Instruments, The Netherlands). The mixture was frozen (−18° C) and thawed again while being shaken vigorously. This procedure was performed three times to assure a median particle size of approximately 15 μm. The concentration of dissolved BAB in the suspension was 180 μg/ml (*p*H, 6.5). The partition coefficient of BAB in a octanol/phosphate-buffer (*p*H, 7.4) was 1028 ± 51 at room temperature; thus, BAB was shown to be a very lipid-soluble drug. (The partition-coefficient of bupivacaine in an octanol/phosphate-buffer [*p*H, 7.4] is only 62 ± 3.)

Animals and Experimental Protocol

Eleven dogs of either sex (weight, 8–15 kg) were cared for in accordance with the guidelines provided by the International Association for the Study of Pain.[5] The protocol was in agreement with the Dutch law on animal experimentation and was approved by the Institutional Animal Care and Use Committee.

All epidural punctures were performed after inducing anesthesia in the dogs *via* mask with O_2/N_2O (50/50) and halothane. The epidural space was entered with either a 16-gauge (epidural catheter insertion) or 20-gauge (single shot) Tuohy needle using the loss of resistance technique (fig. 1). The dogs were awakened after insertion of the epidural catheter or injection of BAB. Sensory tests were performed after complete recovery from anesthesia.

BAB-Injected Dogs. On day 0, an epidural catheter was introduced in six dogs at the L7–S1 interspace and advanced 2.5 cm cephalad. After complete recovery from anesthesia, doses of 0.25%, 0.5% and 1.0% lidocaine, respectively, were administered *via* the catheter at 2-h intervals. The dose (in ml) for both lidocaine and BAB was calculated using the following equation: $y = 0.13 \times -3.8$, where y = dose in ml and x = length between the occiput and base of the tail in cm.[6] Such a volume, lumbosacrally administered, has been shown to distribute up to the level of Th_{12}. After the administration of 1.0% lidocaine, the epidural catheter was removed.

On day 1 and day 3, one-half of the dose (calculated from the formula above) of 2% lidocaine and the full calculated dose of the 10% BAB suspension (range, 3.2–4.5 ml) was injected epidurally at the L7–S1 interspace as a single injection. Lidocaine was administered to confirm clinically that a successful epidural injection was made. Also, on day 1, the ulnar nerves were located using a nerve stimulator and subsequently infiltrated fanwise with 2 ml of BAB 1 to 2 cm proximal to the medial epicondyle of the right forelimb.

On day 7, an epidural catheter with a single distal hole was advanced up to the level of L3. This was confirmed radiologically using 1 ml lopamidol (40 mg/ml). One-half of the calculated volume of 10% BAB was injected at this level and, after partial withdrawal, the other half at the level of L5 (fig. 1).

Control Dogs. Five control dogs were given 0.025% polysorbate 80 in 0.9% NaCl without BAB epidurally following the protocol described above (fig. 1). In contrast to BAB-injected dogs, polysorbate 80 was not locally infiltrated around ulnar nerves.

Functional Evaluation of the BAB-injected Dogs. Motor function and overall body function were evaluated daily during the study. Motor function was evaluated by noting any disturbances of locomotion while the dog was moving in different gaits. The presence of an ataxic gait or paresis of the hind limbs was interpreted as partial motor blockade. Inability to stand on the hind limbs or posterior paralysis was interpreted as complete motor blockade. The animals were observed continuously from the moment of injection to complete motor recovery.

Before the administration of any drug on day 0, the control stimulation threshold was determined by observing the response to an electrical stimulus. This procedure was started with a single rectangular pulse of 1 V and 0.1-msec duration that was generated by a constant volt-

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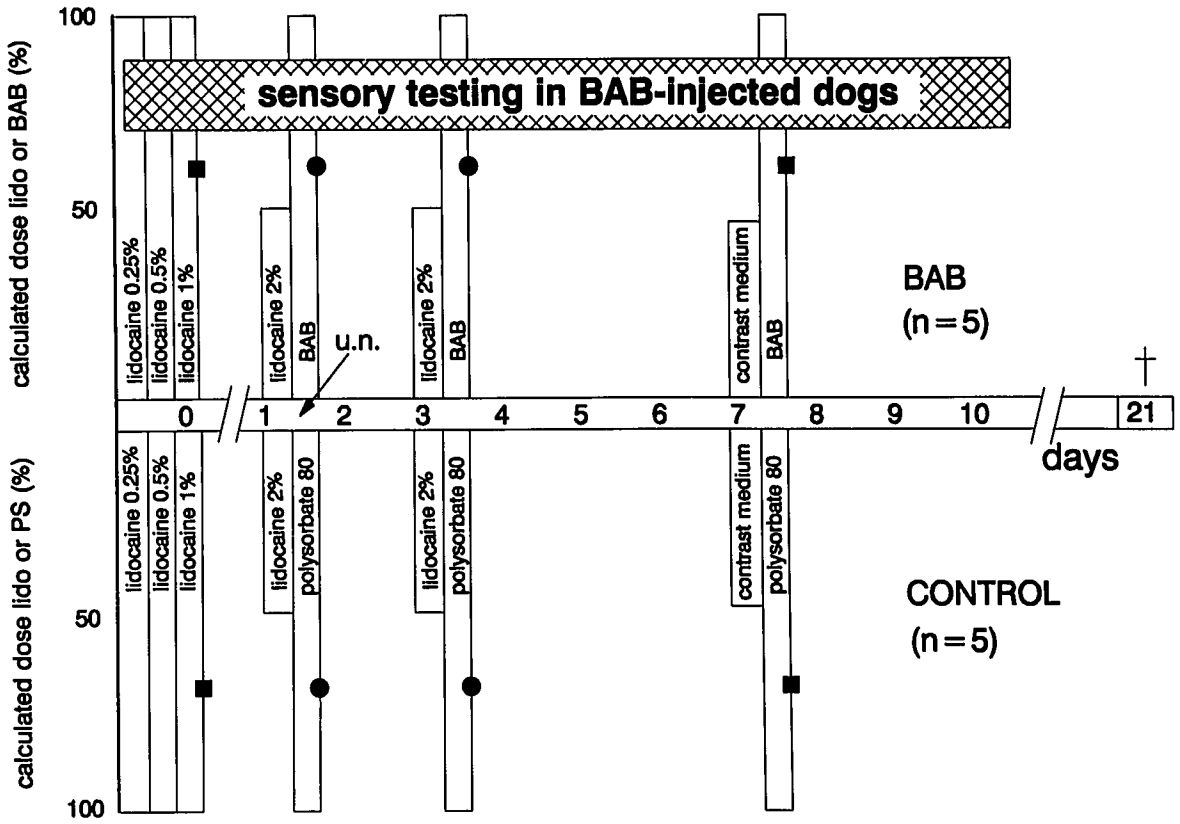

FIG. 1. Study protocol. ■ = epidural injection *via* catheter; ● = epidural injection *via* Tuohy needle; u.n. = infiltration of ulnar nerve with 2 ml BAB.

age stimulator. The stimulus, which was increased in 1-V steps, was applied using two stainless steel needle electrodes. The electrodes were placed subcutaneously at an inter-electrode distance of 1 cm at the distal dorsal side of the hindpaw of the animals. The voltage at which the dog flexed its hindlimb was noted as the stimulation threshold. On day 0, stimulation thresholds were determined before and 30 min after epidural administration of 0.25%, 0.5%, and 1.0% lidocaine, respectively. Three hours after each BAB administration, sensory testing was performed and repeated daily for a period of 10 days following the first BAB administration. Since it has been reported that dogs become rapidly conditioned to such testing, the sensory evaluation was limited to testing once a day.[7]

Pathomorphologic Evaluation. All dogs were killed on day 21 by an overdose of sodium pentobarbital. Routine necropsy was performed. After opening of the cranium and bilateral segmental laminectomies of the vertebral column, the brain, spinal cord with nerve roots, and ulnar nerves (BAB-injected animals only) were rapidly removed and placed in fixative (4% buffered formaldehyde solution) for gross and light microscopic examination. Coronal sections of the brain, cross-sections of the spinal cord, and cross-sections and longitudinal sections of the nerves were embedded in paraffin, cut into 5-μm sections, and stained with hematoxylin and eosin.

Histopathologic analysis was performed first with encoded samples and then repeated blindly. The severity of the pathomorphologic changes observed were graded semiquantitatively from 0 to +++ as follows: +, ++, or +++ indicated that pathomorphologic changes were observed in less than 10%, between 10 and 30%, or more than 30% of the sectioned surface area, respectively.

Statistical Analysis

Statistical analysis of the stimulation threshold data was performed using the paired, two-tailed Student's t test. These data are reported as mean ± SEM. A $P < 0.05$ was considered statistically significant.

Results

All injections were accomplished without complications with one exception: approximately 10 s after injection of 4 ml of BAB, one dog had an opisthotonus and convulsions during 3 min that was followed by apnea. Despite artificial ventilation, it did not regain consciousness after 90 min

and was killed. Necropsy revealed an intrathecal hemorrhage caused by the injecting needle.

Functional Evaluation of BAB-Injected Dogs

None of the animals showed paresis after injection of 0.25% epidural lidocaine. All five animals showed posterior paresis after 0.5% lidocaine. Posterior paralysis was found in three dogs after administration of 1% lidocaine, and two showed posterior paresis. The effects wore off after 1 h. The mean control stimulation threshold was 9 ± 3 V. The mean increase in stimulation threshold after increasing doses of lidocaine, as compared to controls on day 0, were 24% after 0.25% lidocaine ($P > 0.05$), 72% after 0.5% lidocaine ($P < 0.02$), and 212% after lidocaine 1.00% ($P < 0.02$; fig. 2).

The increases in stimulation threshold after administration of BAB, as compared to controls on day 0, were 1% on average for day 1 and day 2 ($P > 0.05$), 18% on average for day 3 through day 6 ($P > 0.05$), and 96% on average for day 7 through day 10 ($P < 0.03$; fig. 2). The increases in stimulation threshold from day 7 through day 10 were comparable to the effect of lidocaine in a concentration between 0.5% and 1% (fig. 2).

All animals demonstrated a period of hindlimb weakness after epidural injection of 2% lidocaine and BAB on day 1 and day 3. These effects wore off after 1 h. All animals also showed hindlimb weakness on day 7 after injections of BAB without lidocaine at L3 and L5. This effect wore off after approximately 1 h in three dogs. Two dogs, however, showed an ataxic gait during the entire observation period (6 h) that day.

Although significant changes in response to the stimulus voltage were observed from day 7 through day 10 (mean increase from 9–18 V after the third epidural BAB injection), all animals had resumed normal activity the day after BAB administration without evidence of altered gait, pain, or difficulty with urination or defecation. None of the dogs showed loss of appetite during the study. No animal showed weakness in the forelimbs during the study.

Pathomorphologic Findings

Routine necropsy results did not reveal abnormalities in any of the dogs. After opening the spinal canal, in two of the five BAB-injected dogs, the epidural tissues of the lumbosacral region showed slight hyperemia that was indicative of a reaction (table 1).

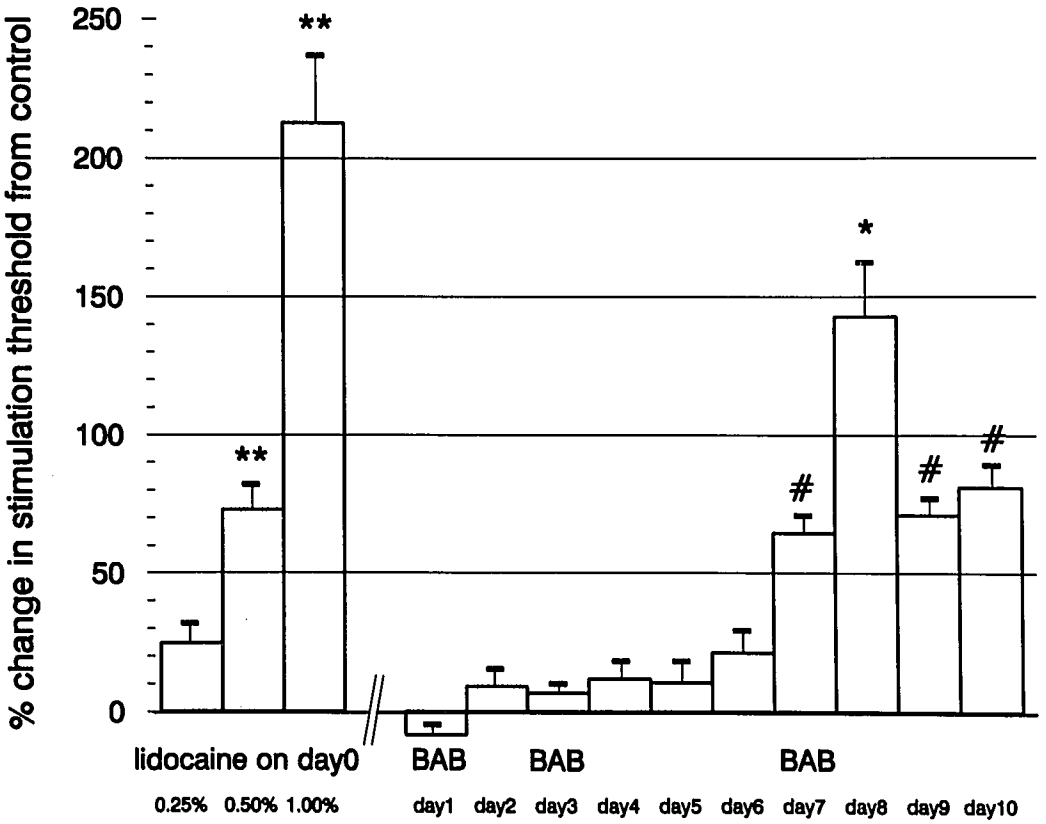

FIG. 2. The effects of epidural lidocaine 0.25%, 0.50%, 1%, and BAB on the stimulation threshold (expressed as percentage change from control; mean ± SEM). *$P < 0.03$, **$P < 0.02$, *$P < 0.01$.

TABLE 1. Pathomorphologic Findings After Epidural Injections of BAB

Dog	Epidural Inflammatory Lesions	Spinal Cord Degeneration Dorsal Columns	Dorsal Spinal Nerve Roots	Ventral Spinal Nerve Roots	Cauda Equina Inflammation
1	+	+	++	+	+
2	+	+	++	+	+
3	0	+	++	+	++
4	+	+	++	+	++
5	+	+	++	+	++

On histologic examination, no brain lesions were found. In lumbar epidural, perineural, and some leptomeningeal areas of four BAB-injected dogs (table 1), inflammatory infiltrations were seen. These infiltrations contained groups of pigment-laden macrophages that were intermingled with lymphocytes. Lumbar and sacral nerve roots of all BAB-injected dogs showed pathomorphologic changes. These changes predominated in the dorsal spinal nerve roots (figs. 3 and 4), but in some areas, the ventral roots showed lesions as well. There was evidence of local demyelination, edema, axonal swelling, and disruption. In these areas, an increase of mononuclear cells (macrophages and Schwann cells) in the neural tissue was prominent. The lesions had developed at the outer aspect of the nerve roots and did not comprise more than 30% of the sectioned surface areas. Slight but evident signs of white matter degeneration were prominent in the endthoracic and lumbosacral dorsal columns in the spinal cords of all BAB-injected animals (fig. 5). Dorsal root ganglions did not show pathomorphologic changes. Some perineural macrophages were found around the ulnar nerves. The ulnar nerves did not show pathomorphologic changes.

The five dogs used as controls (polysorbate 80 in 0.9% NaCl only) showed no signs of induced degeneration or reactive infiltration.

Discussion

The principal findings of this study were long-lasting sensory blockade after epidural BAB administrations without long-lasting motor effects and consistent pathomorphologic changes in dorsal spinal nerve roots and dorsal columns. Ventral roots showed pathomorphologic changes as well, but this finding was less pronounced.

The pathomorphologic findings in our study are in contrast with the findings of Shulman who demonstrated the absence of changes in the CNS after repeated epidural BAB administration.* We have no explanation for this difference. In Shulman's study, the histologic method was not described. A difference in histologic methods therefore cannot be ruled out as a cause of the discrepancy. Shulman used polyethylene-glycol 3350 as suspending agent, and we used polysorbate 80. We demonstrated that polysorbate 80 did not induce pathomorphologic changes. Furthermore, no difference in concentration of dissolved

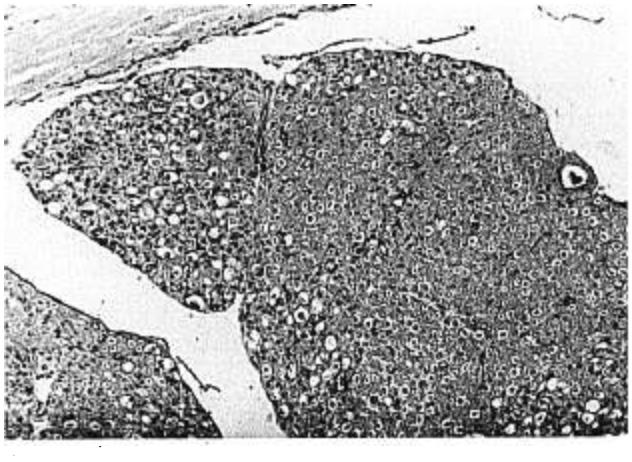

FIG. 3. BAB-injected dog 4, L_4: intrathecal section of dorsal root (hematoxylin and eosin, ×37.5). Note reactive hypercellularity, especially at the outer aspect of the nerve.

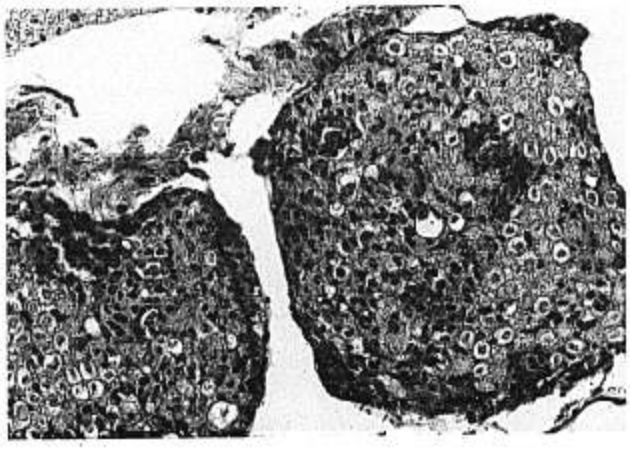

FIG. 4. BAB-injected dog 4, L_4: enlargement of section in fig. 3 (hematoxylin and eosin, ×150).

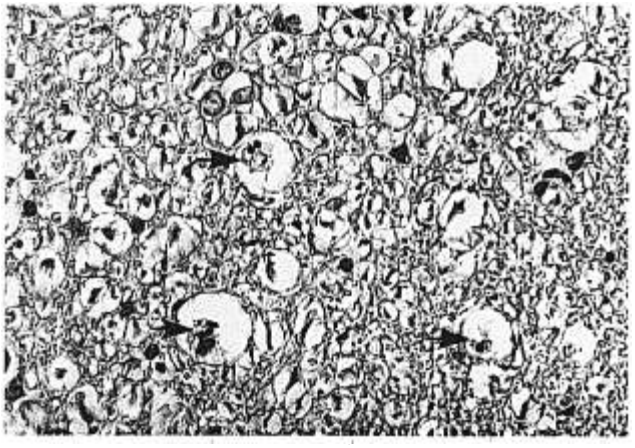

FIG. 5. BAB-injected dog 2, L_2: dorsal white matter showing glia cell reaction and widened digestion chambers with macrophages (arrows), indicating ascending secondary (Wallerian) degeneration (hematoxylin and eosin, ×150).

BAB existed between our and Shulman's suspension. From this, we conclude that neither the suspending agent nor the amount of BAB dissolved was responsible for the differences in findings. It is not likely that polyethyleneglycol 3350 protected the CNS and associated structures since it was shown by Wood *et al.*¶ that certain brands of steroid suspensions containing 2.9% polyethylene-glycol caused demyelination and neurolysis when injected perineurally in rats.

The reasons to use polysorbate 80 in our study were twofold: 1) we were not satisfied with the quality of the BAB suspension prepared with polyethylene-glycol 3350, and 2) polysorbate 80 is used in corticosteroid suspensions, which are generally applied epidurally in humans without reported sequelae. The LD50 of polysorbate 80 in rats is approximately 700 mg/kg after intravenous administration.[8] We used only 3 mg polysorbate 80 in each dog. We demonstrated that the pathomorphologic changes were not induced by polysorbate 80 or the experimental protocol. We postulate that BAB is neurotoxic, but the possibility that the neurotoxic effect stems from combining BAB with 0.025% polysorbate 80 in NaCl 0.9% cannot be excluded.

Significant long-term increases in stimulation thresholds were recorded after repeated BAB administrations, whereas no long-term motor function impairment was observed. This result is consistent with the finding that the pathomorphologic changes are located mainly in the dorsal spinal nerve roots and in the white matter of the dorsal columns. It is hazardous, however, to make a comparison of neurologic function and histologic abnormality, since it is not certain that functional deficits can be explained by histologic abnormality. Other investigators found no correlation between neuropathologic changes and the extent and type of functional loss.[9,10] Furthermore, functional deficits due to changes of the ventral roots may have stayed beyond clinical detection, since the evaluation of motor function was done only by observation of the dog while walking in different gaits. This is not a very sensitive test for evaluating motor blockade.

The finding that the pathomorphologic changes are mainly located dorsally is difficult to explain, since major anatomic differences between ventral and dorsal spinal nerve roots do not exist. A possible explanation may be that BAB is mainly confined to the dorsal epidural space. By comparison, it is noteworthy that in humans the epidural space is a potential space and that injected resin is predominantly situated in the dorsomedial and dorsolateral regions of the epidural space.[11,12] From human anatomy, it is also known that the dorsal nerve roots run in the epidural space over a longer distance than the ventral roots and that the epidural fat is mainly located dorsally.**[13] Since BAB is very lipid soluble, we postulate that BAB is mainly confined to the dorsal epidural space. Data on these features in the dog are not available, so it remains to be determined whether these aspects can explain the finding that changes are mainly located dorsally. The cell bodies of the dorsal spinal nerve roots are located in the spinal ganglions. When dorsal spinal nerves are injured (*e.g.*, the epidural and intrathecal part of the dorsal spinal nerves), an ascending degeneration (Wallerian degeneration) will occur in the spinal cord, since the axons are separated from their cell bodies in the spinal ganglions. The cell bodies of the ventral spinal nerve roots are located in the gray matter of the ventral horns; therefore, Wallerian degeneration will be found in peripheral nerves when ventral intrathecal or epidural spinal nerve roots are injured.

The pathomorphologic changes can be explained by assuming a neurolytic effect of the local anesthetic BAB. The extremely high lipid solubility of BAB promotes uptake in the myelin surrounding the axons of A and B nerve fibers and subsequently in the axons themselves, leading to high axonal concentration of BAB, as was found with other lipid-soluble local anesthetics.[14] The fact that prolonged exposure of nervous tissue to commonly used local anesthetics produces neurologic deficit, if the dose

¶ Wood KM, Arguelles J, Norenberg MD: Degenerative lesions in rat sciatic nerve after local injections of methylprednisolone in sterile aqueous solution. Regional Anesthesia 5:13–15, 1980.

** Luyendijk W: Canalografie (Thesis). University of Leiden, The Netherlands, 1962.

is large enough, is well-established in animal experiments: the longer the duration of exposure, the worse are the neurological sequelae.[9,10,15] In this respect, it is noteworthy that BAB is extremely lipid soluble, so that high axonal concentrations during a prolonged period of time can be expected.[14] These facts may explain the long-lasting increases in stimulation thresholds seen in the BAB-injected animals. This may also be of value in the treatment of intractable cancer pain, despite the fact that neurologic damage is induced.

We reason that BAB has a neurolytic effect on the axons in the spinal nerve roots, and not on the dorsal root ganglions, because no histologic changes were observed in the dorsal root ganglions. Furthermore, local anesthetics administered epidurally are found only in small quantities in the dorsal root ganglions.[16] The neurolytic effect on the axons in the dorsal spinal nerve roots was extensive enough to produce an ascending secondary degeneration (Wallerian degeneration) that resulted in the white matter degeneration in the dorsal columns found in this study.[17]

Local anesthetic agents produce their effects by different mechanisms. Benzocaine, from which BAB is derived, is thought to act by penetrating the nerve membranes, thereby causing conformational changes, which lead to a decrease in the diameter of the sodium channel by membrane expansion.[18] This mechanism is probably different from that of the commonly used local anesthetics, which are believed to diffuse across the nerve membranes and bind to receptor sites in the interior of the sodium channels. No data are available on the neurotoxicity of BAB, presumably because the drug has been used mainly in ointments and powders that are applied directly to wounds.[19] In 1952, a long-acting local anesthetic, Efocaine, was introduced that consisted of 5% BAB, 1% procaine, 0.25% procaine hydrochloride, and the suspending agents, 78% propylene glycol and 2% polyethylene-glycol 300. Although Efocaine had a prolonged duration of action, serious neurologic complications were soon reported. A subsequent study showed that the complications were probably due to the 78% propylene glycol vehicle. The effects of BAB, however, were not studied separately.[20,21]

The concept that the long-lasting effects are due to the continuous slow release of local anesthetic from the particles in suspension, as suggested by Shulman, may be partly true. However, to explain the observed long-lasting sensory effects, high axonal concentrations of BAB and neurolytic changes in spinal nerves and spinal cord also should be taken into account.

The high-lipid solubility of BAB may be useful for inducing neuropathologic changes in the dorsal spinal nerve roots (selective bilateral chemical rhizotomy), since fat is mainly located dorsally. Furthermore, the 10% BAB suspension has a high shear resistance caused by the particles and therefore cannot move as freely as commonly used local anesthetic solutions in the epidural space. In humans, even a commonly used local anesthetic, injected epidurally, shows only minor horizontal spread into the anterior epidural space.[12,22] We postulate therefore that the particles in the BAB suspension are confined mainly to the dorsal epidural space, thereby reducing the risk of neurolytic changes in the ventral nerve roots.

We think it is imperative, however, to use a test dose and radiologic confirmation of the catheter position using radiopaque dye before injecting BAB epidurally. Intrathecal or intravenous injections result in major neurologic sequelae, as was demonstrated by the untoward reaction in one of our dogs. Similar reactions have been observed by Shulman in the dog and in humans.†

Three weeks after exposure of the ulnar nerves to BAB, pathologic changes were limited to a few macrophages around the ulnar nerves that were indicative of a reactive response. No pathomorphologic changes were found in the ulnar nerves. Myers *et al.* bathed peripheral nerves of rats in local anesthetics by surgically exposing them and injecting the local anesthetic directly beneath the fascia but exterior to the epineurium.[15] They found increased edema and Wallerian degeneration and concluded that the clinically used concentrations of local anesthetics may be neurotoxic. Our technique of perineural infiltration was not precise in comparison with the one used by Myers *et al.*[15] We may therefore have failed to demonstrate a possible neurolytic effect of BAB in peripheral nerves.

In conclusion, we demonstrated that the epidural administration of BAB induces a long-lasting sensory blockade that is comparable to the temporary effect of lidocaine in a concentration between 0.5% and 1.0%, without long-lasting motor blockade. Neurotoxicity of BAB must be taken into account to explain these findings, since reproducible pathomorphologic changes were observed in spinal nerves and dorsal columns.

The current study in dogs does not allow us to predict whether painful stimuli from different origin in the intractable cancer pain patient can be treated successfully by epidural BAB. More research is necessary to define the distribution of BAB in the nervous tissue after its epidural administration and to better characterize toxicity, neurolytic effects, and regeneration of nervous tissue after BAB administrations.

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