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Epidural and Intrathecal n-Butyl-p-Aminobenzoate Solution in the Rat

Comparison with Bupivacaine

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Background: **Epidural administration of an aqueous suspension of n-butyl-p-aminobenzoate (BAB) to humans results in long-lasting sensory blockade without motor block. The dose-response of BAB administered epidurally and intrathecally as a solution was studied in rats to define the local anesthetic properties in an established animal model.**

Methods: **The time course of changes in tail withdrawal latency and motor function were determined in rats after epidural or intrathecal administration of solutions of BAB or bupivacaine. The dose-response relation was determined and median effective dose values were calculated.**

Results: **After epidural and intrathecal administration of BAB solutions, the onset and duration of the antinociceptive action were comparable to bupivacaine. Median effective dose values for tail-withdrawal latency of 6 s or more were significantly greater for BAB. After both routes of administration, BAB clearly affected motor function.**

Conclusions: **When administered epidurally and intrathecally as a solution, BAB is a local anesthetic of relative low potency with onset and duration of action comparable to those of bupivacaine. These findings suggest that the long-lasting action obtained after applying BAB suspension results from the slow dissolution (continuous release) of the solid BAB deposited in the epidural space. (Key words: Anesthetics, local: bupivacaine; N-butyl-p-aminobenzoate. Pharmacodynamics. Anesthetic techniques: epidural; intrathecal.)**

N-butyl-p-aminobenzoate (BAB), a congener of benzocaine, has been used as a local anesthetic since 1923. Because BAB is nearly insoluble in water (approximately 1 g in 7 l), the documented pharmaceutical use of BAB is limited to dermatologic preparations such as dusting powders and ointments. Compared with benzocaine and tetracaine, the potency of BAB after topical application is low.[1#]

Epidural administration of an aqueous suspension of BAB to humans was shown recently to produce long-lasting analgesia (measured in months),[2**] with sensory selective nerve block (characterized by segmental loss of pinprick, pain, and cold sensation) but without motor blockade.[2] In an earlier canine study, the stimulation threshold after repeated administration of BAB suspension increased to a similar extent as the short-lived increase after the epidural administration of lidocaine in a concentration of 0.5% to 1%.[3]

The long-lasting analgesic action obtained after epidural administration of the BAB suspension has been attributed to the slow release of the active compound from the particles of the suspension deposited in the epidural space.[2,3] Other mechanisms, however, including an "intrinsic" long-lasting action of BAB on epidural or intrathecal sensory neurons, have not been excluded,

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because no information is available on the pharmacologic activity of BAB after epidural administration in solution.

This study was designed to investigate the dose-response relation and duration of action of solutions of BAB after epidural and intrathecal administration. We measured tail-withdrawal latency (TWL) and motor score in rats, because this animal model has been used extensively to define local anesthetics and opioids in several formulations.[4-9]

Materials and Methods

Preparation of the BAB and Bupivacaine Solutions

The volume that can be injected in the rat by epidural and intrathecal routes is limited to ±20 μl. To administer the required doses of BAB, solutions had to be prepared in which the concentration of BAB exceeded its solubility in water. Polysorbate 80 (OPG, The Netherlands) was the preferred solubilizing agent because the same agent, although in a much lower concentration, is used to create BAB suspensions.[10]

Test solutions were prepared under aseptic conditions. Weighed amounts of BAB (Abbott Laboratories, Chicago, IL) were dissolved in 0.9% NaCl containing 10% v/v polysorbate 80. Bupivacaine-HCl solutions were prepared by dissolving weighed amounts in 0.9% NaCl (Janssen Research Foundation, Beerse, Belgium). Solutions were filtered through 0.2-μm filters, and the final concentration in the solutions were measured by ultraviolet spectrometry (DU-7500; Beckman Instruments, Mijdrecht, The Netherlands).

Animals

Approval of the Institutional Animal Care and Use Committee was obtained to perform the experiments described. Wistar rats weighing 250 ± 20 g were used, and epidural and intrathecal catheters were placed while the animals were anesthetized. For epidural catheterization, a polyethylene catheter (PE10) was introduced into the epidural space over a length of 0.5 cm cephalad *via* a hole drilled in the fourth lumbar vertebra. When the catheter was fixed to the vertebra, the loose end was tunneled subcutaneously toward the occiput. For intrathecal catheterization, a similar procedure was used except that the catheter was inserted into the subarachnoid space.

The animals were allowed 4 days to recover after catheterization and always had free access to food and water. All experiments and housing after surgery took place in an air-conditioned laboratory (temperature, 21 ± 1°C; humidity, 65 ± 10%).

Rats showing any sign of neurological injury were discarded. After the experiments, in which the animals were used only once, the rats were killed. The position of the catheter tip was verified at autopsy by an investigator not aware of the experimental results. The catheter tip was located correctly in all animals, and we noted no sign of fibrinous tissue reaction around the catheter.

Experimental Design

The rats were randomly assigned to receive an epidural or intrathecal injection of one of the following doses of BAB or bupivacaine:

1. Bupivacaine-HCL: Intrathecal or epidural injection with a constant volume of 20 μl containing a dose of 0 nmol (control group); 35 nmol, 69 nmol, 139 nmol, and 277 nmol of bupivacaine-HCl (0 μg, 10 μg, 20 μg, 40 μg, and 80 μg bupivacaine-HCl)
2. BAB in polysorbate 10%: Intrathecal or epidural injection with a constant volume of 20 μl containing a dose of 0 nmol (control group), 189 nmol (only epidural), 379 nmol, 758 nmol, and 1,516 nmol BAB (0 μg; 36 μg, 73 μg, 145 μg, and 291 μg BAB).

Data were collected from five animals per drug treatment condition. Doses were given on a nanomoles-per-rat basis. To exclude variability due to differences in *p*H, osmolarity, and concentration, the same volume was injected epidurally and intrathecally. The method of epidural and intrathecal injection consisted of administering the volume needed in consecutive steps of 1 μl, taking care that the dead space of the catheter was filled with saline, separated from the local anesthetic by 3 μl air.

Tail-withdrawal latency and muscle tone were scored once before and at 1, 2.5, 5, 7.5, 10, 15, 20, 30, and 60 min after injection. General skeletal muscle tone was scored by manual inspection and visual observation according to the scale proposed by Bromage for humans, which we modified for the rat model as follows; 0 = normal tone, free movement of the hind limbs; −1 = weak hypotonia of the hind limbs/body posture; −2 = moderate hypotonia of the hind limbs/body posture; and −3 = inability to support the body on the hind limbs and flat body posture. Tail-withdrawal latency and motor function were scored by an experienced investigator blinded to the drug administered.

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Tail-withdrawal Latency Procedure

The tail-withdrawal reaction procedure used has been described in detail before.[7] Briefly, each rat was placed in a cylindrical holder with its tail hanging freely outside the cage. The distal 5 cm of the tail was immersed in a warm water bath (55 ± 1°C) and the TWL was measured to the nearest 0.1 s. To minimize tissue damage at repeated testing, a cutoff time of 10 s was adopted.

Statistical Analysis

The mean TWL values measured in a control group at any time were tested against the pretreatment mean TWL value of that group by the paired-samples *t* test. Pretreatment mean TWL values of all experimental groups were compared using analysis of variance followed by Scheffé's multiple-range test.

Correlation between dose and (duration of) effect was tested using Spearman's rank test. Onset and time to recovery for antinociceptive action and motor disturbances were defined as the time interval in which the mean TWL and the median motor score of an active treatment group differed statistically for the first or last time from the mean or median value of the control group.

Withdrawal latencies were analyzed per treatment (BAB or bupivacaine/epidural or spinal) at each time by one-way analysis of variance (predictor: dose) followed by Student's *t* test when the analysis was restricted to two means (treatment *versus* control).

Values for motor score were tested for overall statistical differences with the Kruskal-Wallis test followed by the Mann-Whitney U-test, with the two-tailed probability value corrected for ties to reveal differences between drug-treated and control groups.

Median effective dose (ED_{50}) values and 95% confidence intervals were calculated by Probit analysis for the criterion value TWL ≥ 6 s according to Finney's iterative method.[11] The criterion value of ≥6 s, two to three times the pretreatment latency, evolved from studies conducted on large series (thousands) of control rats and has been used as a measure of analgesia in studies of opioids and local anesthetics.[4,7-9] Relative differences between ED_{50}s were tested using the Student *t* test for independent samples (two tailed). The standard errors of the log ED_{50}s were obtained from the 95% confidence limits.[12]

The duration of action of local anesthetics is proportional to the logarithm of the injected dose.[13] The mean duration of TWL ≥ 6 s (TWL6T) was plotted *versus* log dose and fitted to the following equation: TWL6T = A + (1/k)log dose. From the slope (1/k) the half-life ($t^1/_2$) was calculated as $t^1/_2 = k/0.693$.[14,15]

Differences were considered significant at $P < 0.05$.

Results

In the control groups, mean TWL increased significantly from approximately 2 s at t = 0 min to 3.4 s at t = 60 min ($P < 0.05$), but no individual value exceeded 5 s. The motor score was at all times zero. In the active treatment groups, all individual pretreatment TWL values were less than 4 s and all motor scores were zero. No significant differences in the mean pretreatment TWL were found between the experimental groups (active and control).

Epidural Administration

At the lowest dose, BAB did not affect the TWL. The onset of action after higher doses of BAB was within 1 min after injection. After administration of the lowest dose of bupivacaine, the onset was 1-2.5 min; after higher doses it was within 1 min. The antinociceptive effect after epidural administration of BAB increased to 15-20 min after both 758 and 1,516 nmol; after administering bupivacaine, the duration increased to 10-15 min after the dose of 277 nmol (fig. 1).

For both BAB and bupivacaine, the mean duration of TWL ≥ 6 s showed a significant correlation with log dose (fig. 2). The half-lives, calculated from the slopes of the regression lines (TWL6T = A + (1/k)log dose) were, respectively, 2.3 min (SD = 1.5 min) and 2.2 min (SD = 0.4 min) for BAB and bupivacaine and were not significantly different.

The ED_{50}s for BAB were at all times significantly greater than the ED_{50}s for bupivacaine (fig. 3). The lowest ED_{50} after BAB occurred at t = 5 min and for bupivacaine at t = 1-2.5 min, corresponding to the time after injection when the maximum effect on TWL was obtained.

Epidural administration of 189 nmol BAB did not affect motor function. After administering the higher doses, motor disturbances occurred within 1 min. The time to recovery increased from 5-7.5 min after the dose of 379 nmol BAB to 10-15 min after the dose of 1,516 nmol. Bupivacaine at 35 nmol did not induce motor deficits. At higher doses, motor disturbances occurred within 1 min. The maximum effect and the recovery time increased dose dependently (fig. 1).

The motor score time graphs show that the maximum effect on motor score decreases dose dependently in

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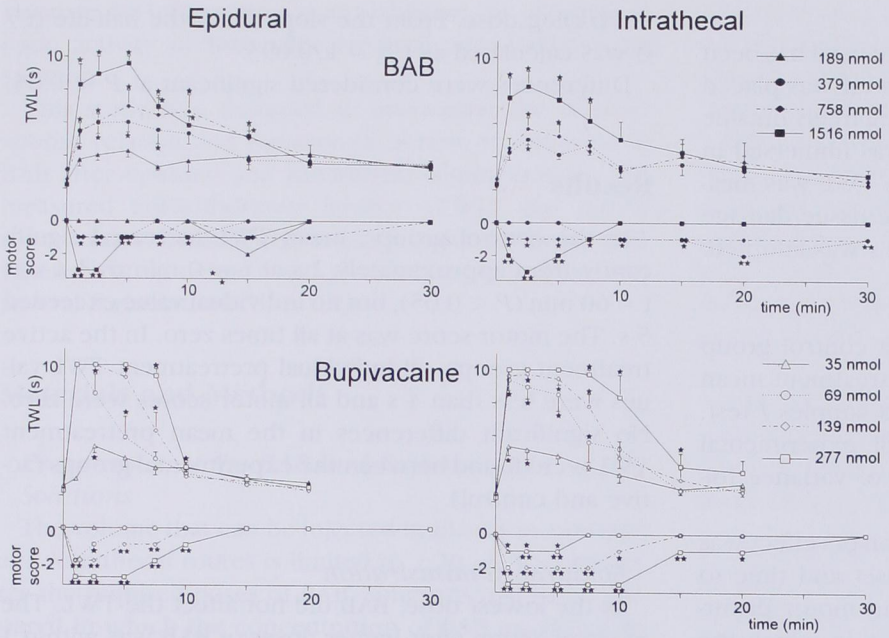

Fig. 1. The time course of changes of the mean tail withdrawal latency (± SEM) and median motor score after epidural and intrathecal administration of various doses of n-butyl-p-aminobenzoate (*upper, closed symbols*) and bupivacaine (*lower, open symbols*). All groups contained five rats. Significant difference of the mean tail withdrawal latency and median motor score determined in an active treatment group *versus* the control group are indicated by $^{*}P < 0.05$ and $^{**}P < 0.01$.

the following order: 277 nmol bupivacaine > 1,516 nmol BAB > 139 nmol bupivacaine > 69 nmol bupivacaine > 758 nmol BAB > 379 nmol BAB > 189 nmol BAB = bupivacaine 35 nmol = control.

Intrathecal Administration

The onset of antinociception after administration of 379 and 758 nmol BAB was 1-2.5 min; after 1,516 nmol it was within 1 min. All four bupivacaine doses tested induced an antinociceptive effect within 1 min. The effect on time to recovery was dose related for BAB and bupivacaine. For BAB, the time to recovery increased from 2.5-5 min after 379 nmol to 7.5-10 min after 1,516 nmol; for bupivacaine from 2.5-

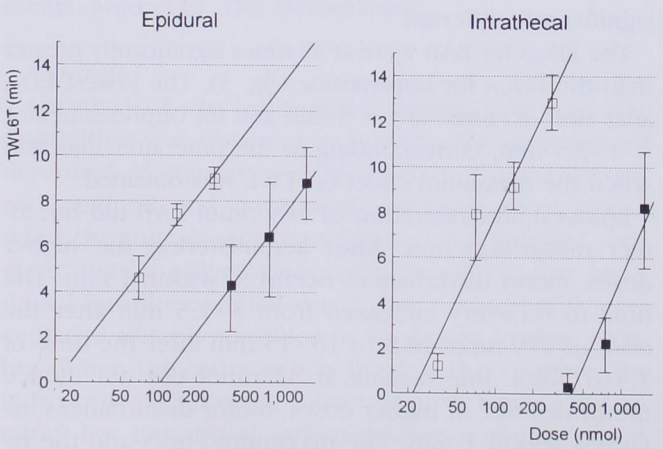

Fig. 2. Plot of the duration of mean tail withdrawal latency ≥ 6 s (TWL6T ± SEM) *versus* log dose and regression lines after epidural and intrathecal administration of n-butyl-p-aminobenzoate (*closed squares*) and bupivacaine (*open squares*).

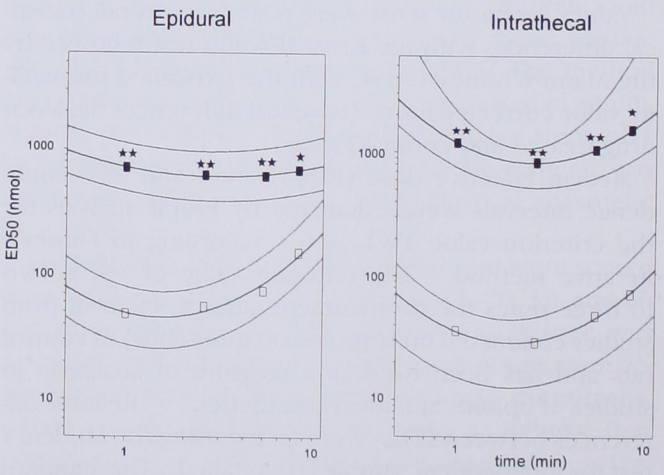

Fig. 3. Time-related effects of epidural and intrathecal n-butyl-p-aminobenzoate (*closed squares*) and bupivacaine (*open squares*) in the rat. Median effective doses and 95% confidence interval expressed in nanomoles (log scale) are plotted against time after administration. Best-fitting quadratic functions are included. Significant difference between the median effective doses of n-butyl-p-aminobenzoate and bupivacaine at any time are indicated by $^{*}P < 0.01$ and $^{**}P < 0.001$.

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5 min after 35 nmol to 15–20 min after the dose of 277 nmol (fig. 1).

The mean duration of TWL ≥ 6 s showed a significant correlation with log dose (fig. 2). The calculated half-lives are, respectively, 4.1 ± 1.3 min and 3.6 ± 0.6 min for BAB and bupivacaine (not significantly different). Again all ED_{50} values for BAB were significantly greater than those for bupivacaine. The lowest ED_{50} for BAB occurred at t = 2.5 min; for bupivacaine at t = 1–2.5 min (fig. 3).

Motor disturbances occurred within 1 min after intrathecal administration of all four doses of bupivacaine and after the two highest doses of BAB (fig. 1). The maximum effect and the recovery time after BAB and bupivacaine increased dose dependently. After administering the highest dose of BAB, a maximum effect on the motor score was seen after approximately 2.5 min. The time courses of the motor score indicated that the maximum effect on motor score decreased in the following order: 277 nmol bupivacaine ≥ 139 nmol bupivacaine ≥ 1,516 nmol BAB > 69 nmol bupivacaine = 379 nmol BAB > 758 nmol BAB > 35 nmol bupivacaine > control.

Discussion

The results of this study provide evidence that after epidural and intrathecal administration as a "true solution" to rats, BAB is characterized as a local anesthetic of relatively low potency. After equipotent doses, the onset and duration of action are comparable to those of bupivacaine.

The ED_{50} values reported for BAB and bupivacaine in our study were obtained by probit analysis for the criterion value TWL ≥ 6 s. These values are valid for the positioning of BAB relative to bupivacaine but are not comparable to other ED_{50} values obtained using other criterion values or by the more generalized E_{max} approach.††

The TWL and motor score measured in the control groups and the pretreatment values measured in the active treatment groups correspond with the results obtained in large groups of control animals.[4,16] Ten percent (v/v) polysorbate 80 in normal saline injected epidurally and intrathecally in a dose of 20 μl did not significantly alter TWL and motor function compared with normal saline. Therefore the effects observed after administration of BAB solutions can be attributed to BAB, not to the solvent.

When extrapolating our results obtained in rats to the results obtained in dogs and humans, species and measurement technology differences should be considered.

In the earlier BAB suspension study in dogs, antinociception was assessed by the limb-withdrawal reaction to an electric stimulus. The effect of the BAB suspension was quantified relative to the effect of lidocaine solutions.[2] In humans, the dermatomal level of analgesia after epidural administration of the suspension was tested by loss of pinprick and cold discrimination; pain control was quantified by the reduction in analgesic drug consumption.[3] In the present solution study in rats, we expanded the range of testing methods by measuring the TWL, a nocifensive reaction test long used to study analgesic drugs.[4–9] In all test methods used so far, despite the differences in physiologic mechanisms and classes of neurons involved, a definite antinociceptive effect of BAB was measured.

Absolute potency for antinociceptive and toxic effects varies considerably among species; relative potencies, on the other hand, seem to be comparable.[17–20] In this study, the relative potency of BAB after epidural and intrathecal administration to rats as a solution is low, which is consistent with findings after topical application to humans.[1,#]

Our results obtained after administering the BAB solutions must be extrapolated with caution to the effects measured after administering the BAB suspension, for the reasons outlined.

Pharmacokinetic parameters also vary considerably among species. Bupivacaine clearance is greater in dogs than in humans, whereas in rats, pipecolyl-xylidide, contrary to the metabolism in humans, is further metabolized to 4-hydroxybupivacaine.[17,19] In general, total-body clearance of amide local anesthetics is greater in animals than in humans, but in all species bupivacaine is classified as "long acting."[17,18] For BAB, no comparative data are available, but studies with other ester local anesthetics show that metabolism by pseudo-cholinesterase in the rat is slow compared with dogs and humans.[21] Such species differences may imply that although in the present study in rats no difference in

†† One of the conditions for comparing ED_{50} values from different studies is that the same quantitative pharmacologic effect is measured. Values of ED_{50} calculated by probit analysis (quantal dose response) are only valid for the specific end point of drug action chosen (our study TWL ≥ 6 s). The use of other end points or graded dose-response analysis (E_{max} concept) may lead to other numeric values.

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duration of the pharmacologic effects was observed between bupivacaine and BAB, in dogs and humans the duration of action after BAB may be even shorter than after bupivacaine.

The main reason for studying the effects of BAB solutions after epidural and intrathecal administration is to (indirectly) clarify the contribution of the pharmaceutical formulation to the observed long-lasting analgesic effect in humans and dogs after repeated epidural administration of the BAB suspension.[2,3**] In the suspension studies, the following pharmacodynamic profile was observed: The antinociceptive effect increases gradually in time until after several days the magnitude of the effect equals the temporary effect measured after administering lidocaine-HCl in a concentration between 0.5% and 1%[2,3] (comparable to the effect of bupivacaine-HCl, 0.125-0.25%[19]). The antinociceptive effect may last for several months (as long as 6 months in humans[3,4]) and is not accompanied by motor blockade.[2**] The opposite profile evolved from our current study when BAB solutions were administered.

These differences in pharmacodynamic time profiles are consistent with our hypothesis that, although BAB is not an intrinsically potent, long-acting local anesthetic (this study), continuous release (dissolution) from the epidural depot of solid BAB in time will, due to the physicochemical properties of BAB (low negative logarithm of the acid ionization constant and low partition-high distribution coefficient[10]), result in accumulation of BAB in the sensory neural structures in concentrations high enough to explain the observed effects. Thirty-six days after administering the BAB suspension to patients, solid BAB deposits were still clearly present in the epidural compartment at necropsy.[22]

The occurrence of dose-dependent motor block after epidural and intrathecal administration of BAB as a solution is similar to the effects of other local anesthetics.[17,19] However, BAB administered epidurally as a suspension did not produce motor block.[2,3**] The major difference between BAB administered as a suspension and BAB administered as a solution (this study) is the concentration of dissolved BAB (1 μM in the suspension *versus* 9.5-75.8 μM in the solution). We hypothesize that the low concentration of dissolved BAB, available in BAB administered as a suspension, results in a low concentration gradient toward cerebrospinal fluid; that is, in limited diffusion through the dura-arachnoid space. This concentration effect is enhanced by the fact that the permeability of the dura-arachnoid barrier for BAB is low compared with other local anesthetics.‡‡,§§ Furthermore, because BAB contains an ester bond, any BAB entering the cerebrospinal fluid will be subject to inactivation by cholinesterase(s), thus helping to decrease the concentrations of BAB in the cerebrospinal fluid. In serum this hydrolysis proceeds at a high rate.[23-25]

Cholinesterase activity in cerebrospinal fluid is low compared with serum (in humans, 2-6.5 U/l *versus* 550-1,675 U/l),[26] but this reaction will nevertheless result in lowered concentrations and faster clearance of BAB from cerebrospinal fluid. We postulate that by these mechanisms the sensory selective effect will not be nullified by the "buildup" of an active concentration of BAB in cerebrospinal fluid.[27-31] After epidural administration as a solution, diffusion will proceed at a rate 10-75 times faster (proportional to the concentration gradient), resulting in equivalently higher cerebrospinal fluid concentrations and consequently in a more intense motor block.

In conclusion, the pharmacodynamic profile of BAB, administered epidurally and intrathecally as a solution, suggests that the long-lasting action obtained after applying BAB suspension in humans results from the slow dissolution (continuous release) of the solid BAB deposited in the epidural space. The selective effect on sensory fibers observed after administering the suspension can be explained by the low concentration of dissolved BAB in the suspension, preventing "active" concentrations in motor neurons, both in the epidural space and in cerebrospinal fluid.

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