Effect on intracranial pressure of furosemide combined with varying doses and administration rates of mannitol

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The first part of this study investigated the combined use of furosemide and mannitol in the treatment of elevated intracranial pressure (ICP). Two groups of dogs were studied to determine if renal excretion of mannitol was altered in the presence of furosemide. No significant difference in excretion was noted between the two groups. Fifteen animals were used in other studies to identify the most advantageous sequence of administration of furosemide and mannitol. Infusion of mannitol followed by furosemide 15 minutes later resulted in the most profound and sustained ICP reduction. The effect on ICP reduction of varying the mannitol dose was observed in studies using single doses of 0.5 gm/kg, 0.75 gm/kg, and 1 gm/kg. The larger mannitol dose, resulting in a greater blood-brain osmotic gradient, proved to be the most efficacious in ICP reduction. A further 15 animals were used in investigations to determine whether changing the rate of delivery of the most effective mannitol dose (1 gm/kg) influenced resultant ICP reduction. The results indicated that rapid administration (2 ml/kg/min) produced higher peak serum concentrations of mannitol and more profound lowering of ICP than the same dose delivered at slower rates.

KEY WORDS • intracranial pressure • mannitol • furosemide • drug delivery • combined chemotherapy • dog

The use of diuretic agents for the reduction of elevated intracranial pressure (ICP) has been found to be effective and is widely recognized as a suitable means of management of this condition. Mannitol, an osmotic diuretic, has been commonly used clinically and experimentally for this purpose, either on its own or in combination with other diuretic agents. Previous experimental evidence has shown that mannitol in combination with furosemide, a distal loop diuretic, may be more effective in successfully reducing elevated ICP and in sustaining this reduction than results with either agent alone. It has been suggested that establishment of a reversal of the blood-brain osmotic gradient with mannitol and prolongation of this favorable gradient by the potent action of furosemide upon the distal renal tubules may be the mechanism by which these agents act synergistically.

If it is assumed that establishment of a favorable blood-brain osmotic gradient induced by mannitol is a mechanism whereby brain water is removed and ICP is reduced, there arise several questions regarding factors that may influence the outcome of this therapy. Does the presence of furosemide change the usual manner of excretion of mannitol by the distal tubules? Does the sequencing and timing of mannitol and furosemide administration have an influence on the efficacy of treatment? If the reduction of ICP is a function of the blood-brain osmotic gradient, can the response be altered by varying the dose of mannitol? Finally, if a dose of mannitol that is most effective can be identified, does the rate of administration of this optimum dose have any influence on ICP reduction?

This study was undertaken in an attempt to address these questions, which would appear to be pertinent in consideration of treatment of elevated ICP using these diuretic agents.

Materials and Methods

Animal Preparation

Fifty-five adult mongrel dogs, each weighing between 15 and 30 kg, were used in this series. The animals received ketamine (10 mg/kg) and xylazine (1 mg/kg) initially, and intubation and mechanical ventilation were performed 15 minutes later. Anesthesia was maintained with 1.5% halothane, and the animals were paralyzed with pancuronium bromide (0.1 mg/kg).
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Following induction of anesthesia, the surgical preparation of the animals was performed in the following manner. The femoral artery was cannulated to provide a means of continuous monitoring of systemic arterial blood pressure and for the periodic withdrawal of blood samples for measurement of arterial blood gases and pH. The femoral vein was similarly cannulated to allow for intravenous infusion of medication. A urinary catheter was introduced for urine collection and sampling. Access to the skull was gained via a midline skin incision and reflection of the temporalis muscles, and bilateral 1-cm parietal openings were drilled. An inflatable epidural balloon catheter was placed on one side, and a solid-state Gaetec ICP transducer* was inserted into the subdural space on the opposite side.

During the initial stage of the procedure, the ventilator was adjusted to maintain stabilization of normal blood gases and pH values. These parameters were measured throughout the course of the experiment (mean ± standard error of the mean: pH 7.36 ± 0.05, pCO₂ 33.6 ± 1.8 mm Hg, pO₂ 118 ± 2.9 mm Hg). Blood pressure was monitored continuously, and did not change significantly during the investigation. Incremental epidural balloon inflation was carried out until the elevated ICP was stable for 30 minutes prior to treatment. Once an acceptable elevated ICP was attained, the balloon inflation remained unchanged for the remainder of the experiment. The ICP was increased to between 30 and 40 mm Hg in all cases, and was continuously recorded throughout the time course of the experimental period. Urine output was recorded continually, and periodic measurements of urine and serum osmolarity were taken during the procedure.

Mannitol used in all cases was radiolabeled by the addition of tritiated (³H) mannitol to allow determination of mannitol concentration in serum and urine. Samples containing ³H mannitol activity were solubilized in an Aquasol cocktail and counted with a liquid scintillation counter.† Corrections for background and quench were made as required. The concentrations of mannitol were calculated from the specific activity of the samples.

Experimental Groups

Eleven groups of animals (five in each group) were used in this series of experiments after being prepared as described above (Table 1). Group 1 dogs received mannitol (1 gm/kg) alone and Group 2 the same dose of mannitol (1 gm/kg) followed by furosemide (0.7 mg/kg) 15 minutes later. Serum and urine mannitol concentrations were periodically obtained allowing comparison of the excretion of mannitol in the presence or absence of furosemide.

* Gaetec pressure transducer, Model ICT/b, manufactured by Medical Measurements, Inc., Hackensack, New Jersey.
† Tritiated mannitol and Aquasol cocktail obtained from New England Nuclear, Boston, Massachusetts; liquid scintillation counter, Model LS-9800, manufactured by Beckman Instruments, Palo Alto, California.

The next three groups of animals were used to determine the most advantageous timing sequence of administration of furosemide (0.7 mg/kg) in relation to mannitol (1 gm/kg). Group 3 received a dose of furosemide followed by mannitol 15 minutes later. Group 4 animals were treated by simultaneous administration of both medications. Treatment in Group 5 consisted of mannitol being administered initially, followed by furosemide 15 minutes later.

Three groups of animals were used to determine the effect on ICP reduction of varying the dose of mannitol. Group 6 received mannitol in a dose of 0.5 gm/kg. Mannitol in a dose of 0.75 gm/kg was administered to Group 7. Animals receiving mannitol in the largest dose (1 gm/kg) comprised Group 8. The mannitol administration was delivered as a rapid bolus in each of these three groups of experiments.

The final three groups of animals all received identical doses of mannitol (1 gm/kg), the only difference being the rate of administration. In Group 9 animals the mannitol dose was administered slowly at a rate of 0.25 ml/kg/min. Group 10 received an equivalent mannitol dose delivered at 0.5 ml/kg/min. In Group 11 animals mannitol treatment was administered at a rate of 2.0 ml/kg/min.

All values presented in the figures are given as means ± standard errors of the mean. Levels of significance between experimental groups were determined after a Student t-test: p < 0.05 was considered to show a significant level of difference between two experimental groups.

### Table 1

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Treatment Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim of Experiment</td>
<td>Group No.</td>
</tr>
<tr>
<td>to determine effect of furosemide on excretion of mannitol</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>mannitol (0.7 mg/kg) &amp; furosemide (0.7 mg/kg) 15 min later</td>
</tr>
<tr>
<td>to identify best sequence of diuretic administration</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>simultaneous administration of furosemide (0.7 mg/kg) &amp; mannitol (1 gm/kg)</td>
</tr>
<tr>
<td>5</td>
<td>mannitol (1 gm/kg) &amp; furosemide (0.7 mg/kg) 15 min later</td>
</tr>
<tr>
<td>to observe effect of varying mannitol dose</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>mannitol (0.75 gm/kg)</td>
</tr>
<tr>
<td>8</td>
<td>mannitol (1 gm/kg)</td>
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<tr>
<td>to determine most effective rate of mannitol administration</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>mannitol (1 gm/kg) at 0.5 mg/kg/min</td>
</tr>
<tr>
<td>11</td>
<td>mannitol (1 gm/kg) at 2.0 mg/kg/min</td>
</tr>
</tbody>
</table>

* Each group consisted of five dogs.
Results

Drug Combination and Sequencing

In the first two experimental groups, periodic samples of blood and urine were obtained throughout the 180 minutes of the experimental period for the determination of serum and urine mannitol concentrations. These data are presented in Fig. 1. Serum levels in both groups showed an initial sharp rise following mannitol administration, gradually declining over the course of the experiment. No significant differences in serum mannitol levels were observed in the two groups. Group 1 animals receiving mannitol only showed an initial low urine mannitol concentration, which gradually increased as the effects of diuresis declined. By comparison, the animals that received furosemide in addition to mannitol (Group 2) displayed a marked decrease in urine mannitol concentration as a result of the greatly enhanced diuresis following the dose of furosemide. After the diuretic effect ceased, urine mannitol concentration increased. However, calculation of absolute amounts of mannitol in collected urine samples over comparable time periods in both groups failed to show any significant differences in the manner in which mannitol was eliminated in the urine, whether furosemide was present or not.

The effect of varying the sequence of administration of mannitol and furosemide was compared in Groups 3, 4, and 5. The results, as shown in Fig. 2, indicate that the most profound reduction of ICP (62%) was achieved in Group 5 animals, those receiving mannitol followed by furosemide 15 minutes later. When the mannitol and furosemide were delivered simultaneously (Group 4) a smaller decrease in ICP (52%) resulted, and the duration of the decrease was not as prolonged as in Group 5. When furosemide preceded mannitol administration by 15 minutes, as in Group 3, the resultant ICP reduction was the least pronounced (46%) of the three groups.

Mannitol Dosage

Reduction of elevated ICP with an intravenous bolus of mannitol at three different dosages was compared in Groups 6, 7, and 8. Figure 3 shows the ICP data and the serum mannitol concentrations in these groups. A modest reduction (23%) in elevated ICP resulted from a dose of 0.5 gm/kg, a slightly greater reduction (34%) followed a dose of 0.75 mg/kg, and the most effective reduction of all groups (58%) was observed subsequent to a dose of 1 gm/kg. Serum mannitol concentrations were seen to be proportionate to the dose administered.
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Rate of Mannitol Administration

The results in experimental Groups 6, 7, and 8 indicated that a single dose of mannitol (1 gm/kg) was more effective in reducing elevated ICP than were single doses of smaller amounts. Thus, the animals constituting the final three groups (Groups 9, 10, and 11) were given this most effective dose of 1 gm/kg at differing rates to see if the rate of delivery of identical doses influenced the outcome. Figure 4 displays the ICP record and serum mannitol concentrations in these groups. At the slowest delivery rate (0.25 ml/kg/min), Group 9 animals achieved an ICP reduction of 30%. A 34% decrease of ICP was seen in Group 10 which received the same mannitol dose delivered at 0.5 ml/kg/min. The most effective response, with a 58% reduction in ICP, was seen in Group 11 following infusion of mannitol at a rate of 2.0 ml/kg/min. Figure 4 right shows the record of serum mannitol concentrations in these groups, and clearly indicates the differences in the shape of the curves relative to the rate of mannitol infusion. It can be seen that the highest peak concentration of serum mannitol occurs after the more rapid rate of infusion.

Discussion

Effective use of osmotic diuresis in reduction of brain water and subsequent lowering of ICP has been well documented in numerous clinical and experimen-
Mannitol has particularly gained widespread acceptance as a beneficial agent for the treatment of elevated ICP, and appears to be especially effective if the blood-brain barrier is intact. It is apparent that successful removal of water from brain and extracellular brain fluid is largely due to the osmotic gradient induced by mannitol in favor of passage of water out of the brain and into blood across the cerebral capillaries, with subsequent removal of this water resulting in reduction of volume of the intracranial contents, and hence the lowering of ICP. It has been reported by numerous observers that, when mannitol is used in combination with distal loop diuretics such as furosemide, its therapeutic effect is enhanced to a considerable degree. Several mechanisms of action of furosemide in achieving enhancement of the mannitol effect have been suggested, among them being the effect of furosemide on the production of cerebrospinal fluid and also the inhibition of water and electrolyte reabsorption in the distal renal tubules. The latter is a proven action of furosemide, and in fact the mechanism whereby the diuretic effect of this drug is expressed. We have previously postulated that the renal tubule action of furosemide, resulting in massive diuresis of dilute urine, could help sustain the elevated serum osmolality produced by mannitol, thus prolonging the period of effectiveness of a given mannitol dose. This would appear to be the principal mechanism in the enhancement of response to mannitol administration by the additional employment of a loop diuretic such as furosemide.

In addition to this known mode of action, another possibility could be theoretically considered; namely, does the presence of furosemide alter in any way the manner of excretion of mannitol in favor of longer retention of this agent, thus prolonging its effect? The first part of this study investigated this theoretical possibility. The results indicated that for the same dose of mannitol, serum mannitol levels were not significantly different over the 3-hour observation period in both groups of animals studied, whether mannitol was given alone or in combination with furosemide. Measurement of urine mannitol concentrations in the two groups of experiments (Fig. 1 right) appeared to show a marked difference in urine mannitol content in the group of animals receiving furosemide. However, this should not be misinterpreted, as the apparent disparity can be explained by the very greatly enhanced diuresis induced by furosemide, resulting in larger volumes of dilute urine. Thus, although the concentration of mannitol in the urine is lowered subsequent to furosemide-induced diuresis, if the volume of urine produced over these time periods is taken into account, the absolute amount of mannitol excreted during the timed collection periods is similar in both groups of experiments. This suggests that the renal kinetics of mannitol are not altered by the presence of furosemide and supports the view that the principal role of furosemide in enhancing mannitol action seems indeed to be inhibition of water and electrolyte reabsorption in the distal renal tubules; this results in copious production of dilute urine and prolongation of the mannitol-induced elevation of serum osmolality.

Regarding the sequence of administration of furosemide and mannitol, Fig. 2 displays the ICP response to three different protocols. A combination of osmotic and loop diuresis was administered to all groups using the same dosage of mannitol and of furosemide; the only difference was the sequence in which they were administered. Clearly, the ICP response was greatest when furosemide was given 15 minutes after the intravenous bolus administration of mannitol. When the furosemide dose was given prior to mannitol administration, the ICP response was similar to that following treatment with mannitol alone, and no benefit was gained from the use of furosemide. It appears necessary to establish a favorable blood-brain osmotic gradient with mannitol first in order to initiate removal of brain water and lowering of ICP. Then with the onset of the osmotic diuretic effect of mannitol, the furosemide exerts its greatest effect with enhanced removal of water via the urine with no adverse effect of mannitol clearance. Simultaneous administration of both agents resulted in a similar magnitude of ICP reduction as when the furosemide followed mannitol, but the onset of return toward the baseline ICP began much earlier when simultaneous administration was employed. Thus, the preservation of a favorable osmotic gradient preventing return of water from blood to brain and hence return toward baseline ICP is better facilitated once the initial gradient has been established by the osmotic effect of mannitol.

Reports of the dose-response characteristics of mannitol usage have presented varying opinions as to the optimal dose for the most effective reduction in ICP. In clinical situations it has been reported that larger mannitol doses result in greater reductions in brain bulk and ICP, whereas other reports have indicated that the same magnitude of ICP reduction resulted from differing mannitol doses. The observations reported in the present experimental study suggest that the magnitude of the desired response of reduced ICP is directly related to the amount of the mannitol given. Serum mannitol concentrations in the experimental groups receiving differing mannitol doses (Fig. 3 right) were approximately proportionate to the amount of medication used. Serum osmolality measurements in the three different groups showed a maximum change from baseline mannitol concentration of 41 ± 1.7 mOsm in the group receiving 1 gm/kg whereas a dose of 0.5 gm/kg resulted in a maximum change of only 21.2 ± 1.3 mOsm. The intermediate dose of 0.75 gm/kg produced a maximum change of 32.1 ± 2.1 mOsm mannitol in serum. The greater the concentration of mannitol (higher dose) the greater is the osmotic gradient established at the interface of brain tissue and the cerebral
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capillary. Hence, a larger reduction of brain bulk follows and a greater drop in ICP. This was clearly the case under the conditions of the present experimental study, although it is recognized that in certain clinical situations other factors may be involved that may modify the ICP response.

The most dramatic drop in ICP appears to occur when the magnitude of the blood-brain osmotic gradient is at its greatest in the early stage of mannitol infusion. In the experimental groups receiving identical doses of mannitol at different rates of infusion, the most pronounced decrease in ICP occurred subsequent to the more rapid rate of administration (Fig. 4 left). Observations of serum mannitol concentrations for equivalent time periods for the three rates of infusion used (Fig. 4 right) clearly indicated the difference in times taken to achieve peak serum mannitol concentration. For the rates of infusion used, concentration of mannitol climbed throughout the course of the infusion at each of the three different delivery rates. The difference lay in the rate of increase in mannitol concentration; the slowest rate of delivery resulted in the slowest rate of increase in concentration and also the lowest peak difference from baseline. As the degree of ICP reduction is influenced by the osmotic gradient caused by the presence of mannitol, it is not surprising to find that the more favorable ICP response occurred following the greater serum osmolality elevation induced by the more rapid infusion. Measurable levels of mannitol were detectable in collected urine samples beginning approximately 6 minutes after the infusion started. Consequently, at the lower rates of administration, much of the mannitol is already being excreted via the renal tubules before the entire dose of mannitol has been infused. The full osmotic potential of the mannitol dose is therefore not attained when compared to the same total dose given more rapidly.

Rapid infusion of 25% mannitol in a dose of 1 gm/kg is not without its complications, however. Continuous recording of systemic arterial pressure carried out in these studies consistently indicated a transient fall of 10 to 15 mm Hg in blood pressure during the first 30 to 60 seconds when mannitol was infused at a rate of 2.0 ml/kg/min. This was followed by a rise in arterial pressure above the baseline by 10 to 15 mm Hg during the next 60 seconds, after which the arterial pressure gradually returned to baseline within 5 minutes. Similar observations have been reported1,3,6,8,19 and most recently confirmed by Ravussin, et al.13 These transient changes in arterial pressure were accompanied by a brief increase (60 seconds) in ICP of 10% to 12% above baseline, followed by a rapid decline in ICP past baseline during the next 60 seconds. These transient arterial and cerebrospinal fluid pressure changes were only observed during the course of mannitol infusion at 2.0 ml/kg/min, and did not accompany the slower rates of administration. In clinical situations, the advantages of attaining a rapid elevation of serum osmolality which ultimately reduces ICP to the greatest degree should be balanced against the possible disadvantages of the transient brief rise in ICP that occurs with very rapid mannitol infusion.

In summary, this experimental study sheds some light on the role of furosemide in combination osmotic and loop diuretic therapy for reduction of ICP, in regard to its mode of action and most effective time of administration. It has been demonstrated that acute reduction of ICP can be correlated with the magnitude of the blood-brain osmotic gradient induced by mannitol, and that this gradient is best achieved with larger doses administered at a rapid rate. These observations may be applicable in certain clinical situations.

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