A COMPARATIVE STUDY OF THE EFFECTS OF THE BARBITURATES, ETHER, AND BULBOCAPNINE ON MICTURITION[1]

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INTRODUCTION

From experimental study of the control of micturition in animals it is clear that vesical activity is modified by the use of the common laboratory anesthetics. Barrington (1) noticed this with regard to chloroform and deep ether anesthesia, using as his criterion the ability of the bladder to empty completely. Langworthy and Kolb (2) described a rise in intravesical pressure on enhancing the depth of ether anesthesia. Before proceeding further with more detailed study of micturition it seems necessary to define clearly the modifications of normal function produced by ether and the barbiturates. Furthermore bulbocapnine has been tried, its actions studied, and it has been found to be a valuable addition to the usual laboratory anesthetics.

The present paper deals with a series of records of vesical filling made on normal cats or preparations studied after denervation of the abdominal wall. The latter operation had no influence upon vesical activity as will be shown in another place. These records have been analysed as to the type and dosage of the anesthetic used and certain features in vesical filling and emptying. These were: (*a*) The resting intravesical pressure with the organ empty. (*b*) The rise in resting pressure following addition of increments of fluid. (*c*) The reaction of the vesical wall to sudden stretch. (*d*) The activity of the detrusor muscle during micturition. (*e*) The presence or absence of residual urine.

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METHODS

Thirty-four cats were studied for periods of from one to nine weeks. One hundred and nineteen kymographic records of vesical filling were made on the various animals at seven to ten day intervals.

The apparatus used for obtaining these records has been described previously (3). The animal is catheterised with a fine glass cannula or a ureteral catheter, the bladder emptied and the catheter connected to a T-tube. This leads in turn to a source of fluid and a water manometer recording by a Marey tambour on a kymograph. After the resting vesical pressure is obtained, 5-cc. increments of fluid are added at 45-second intervals, the time recorder registering at 5-second intervals. This interval allows adequate time for the bladder to adapt to a new volume at a resting pressure. The record is terminated when fluid first appears about the catheter which is fixed in the urethra only by the tension of the urethral wall.

Records were obtained without anesthesia by placing the cats in a plaster of paris body cast which allows the limbs to project freely. Nembutal always was injected into the peritoneal cavity and bulbocapnine subcutaneously. As the findings are essentially similar for each anesthetic in the whole group of cats, the graphic records presented are those from a single animal studied over a period of nine weeks following denervation of the abdominal wall.

RESULTS

1. Reading made without anesthesia

Kymographic tracings of vesical filling made from patients without anesthesia by Langworthy, Lewis, Dees and Hesser (3) agree essentially with the record obtained from the unanesthetised cat such as is reported here (fig. 1). The vertical lines upon the tracing indicate the sharp rises in pressure following addition of 5-cc. amounts of fluid into the system. The initial pressure with the bladder empty equaled 3 cm. of water. On adding 5-cc. of fluid a sharp rise of pressure to 40 cm. took

place but immediately fell away to a resting level of 5 cm. Similar increases in pressure resulted on the addition of each 5-cc. increment, but subsided to a slowly increasing resting level as the kymograph record shows. Between the various increments a few spontaneous vesical stretch responses (*A*) may be seen. The sharper and more prominent rises (*B*) were associated with crying which caused increased intraabdominal pressure. After the addition of 65-cc., the resting level equaled 10 cm. Following another 5-cc. increment the animal cried a few times and then

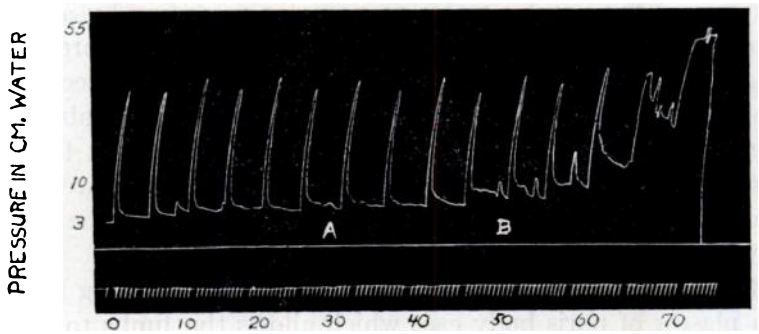

FIG. 1. RECORD OF VESICAL FILLING, ANIMAL UNANESTHETIZED

Pressure in centimeters of water on the abscissae, volume in cubic centimeters on the ordinates. *A* indicates small vesical waves, *B* waves produced by crying. Note the initial low pressure, the slow rise in pressure as filling proceeds, and the strong terminal contraction starting at a pressure of 16 cm. water causing complete emptying of the bladder. Time recorded at 5-second intervals.

a sharp spontaneous increase in pressure to 55 cm. of water occurred. This was associated with strong and precipitous urination. No residual urine was present in the bladder.

2. Ether anesthesia

In this series seven different observations were made using light ether anesthesia. These substantially support the statements of Barrington, and Langworthy and Kolb, and are presented in the accompanying graphs.

The first record (fig. 2) of filling under ether was made two weeks after denervation of the abdominal wall. The resting

pressure was not unusual (2.8 cm.) nor was filling remarkable until 35-cc. of fluid had entered the bladder. Then the resting pressure read at 10 cm. of water. After the addition of the succeeding 5-cc. the resting level reached 21 cm. and finally on the next addition of 5-cc. of fluid a few drops of urine passively ran out about the catheter. The residual fluid in the bladder equaled 40-cc.

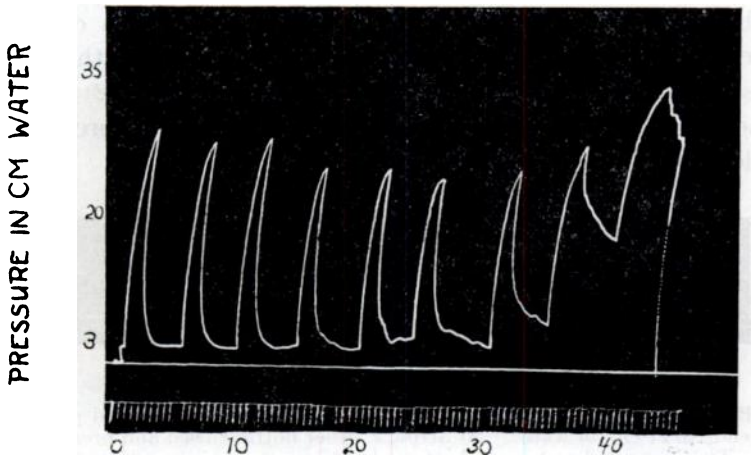

FIG. 2. ETHER ANESTHESIA

The initial pressure is not unusual but as filling proceeds the pressures ascend rapidly in steps until a few drops are forced about the catheter passively at a pressure of 35 cm. of water. Time recorded at 5-second intervals.

In this case fluid was held without loss at a pressure as high as 21 cm., whereas in the unanesthetised animal pressures of 13 to 14 cm. cause active vesical contraction. Again when fluid was passed it came forth as a few drops at a pressure of 35 cm. of water. The drug has definitely depressed active and sustained contraction of the detrusor muscle.

It has to be noted, however, that during induction of ether anaesthesia a strong vesical contraction with urination may occur. Likewise under very light anesthesia active vesical contraction may follow stretch of the bladder wall, but under such

conditions graphic records are usually difficult to obtain due to struggling.

The second kymographic tracing (fig. 3) under ether demonstrates clearly the effects of increasing the depth of anesthesia. The drum was revolving rapidly and the intravesical pressure was steady at 13 cm. of fluid (catheter tied in urethra). A cannula placed in the trachea was connected to a Harvard respirator. An ether bottle was inserted into the system by a series of side tubings. At the arrow (*1*) the direct air line was closed and the air passed over the ether. Within five seconds the pressure rose to 21 cm., an increase of 8 cm. of water. At (*2*) the direct line was opened and the ether system closed. The pressure subsided to 13 cm. in twenty seconds.

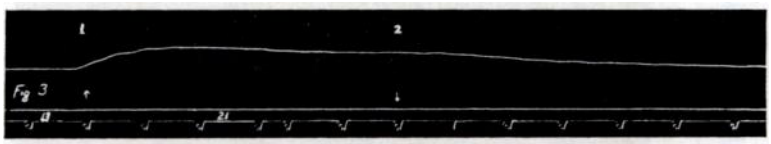

FIG. 3. ETHER ANESTHESIA DURING INDUCTION

Pressure at 13 cm. of water. At arrow *1*, ether bottle opened and pressure ascends to 21 cm. of water. At arrow *2*, ether bottle closed and pressure falls to 13. Time recorded at 1-second intervals.

3. Anesthesia with the barbiturates

Nembutal (Abbott) and Dial (Ciba) were the drugs used in this series. The recent studies have been done exclusively with nembutal but compare exactly with earlier ones under dial anesthesia. These include 65 observations using varied doses of the drug. The average dose was 31 mgm. per kilogram, the maximum 45 mgm. per kilogram, and the minimum 19 mgm. per kilogram.

A kymographic record of one of these observations is shown in figure 4. Here again the initial pressure with the bladder empty equaled 2.8 cm., and after the addition of the first 5-cc. rose to 3.2 cm. The resting pressures remained low (below 7.5 cm.) until 45-cc. were added, and then increased to 11, 15, and 21 cm. after each succeeding increment. On the addition of

5-cc. more a few drops were forced about the catheter at a pressure of 38 cm. of water, but no active vesical contraction occurred. All the fluid was held as a residuum.

In the 68 recordings of vesical filling under nembutal anesthesia contraction occurred only 11 times; and of these only 3 completely emptied the bladder. The dosage per kilogram appeared to have little relationship to the presence or absence of contraction when successive readings were taken on different days over a period of time. Only in two instances did active contraction

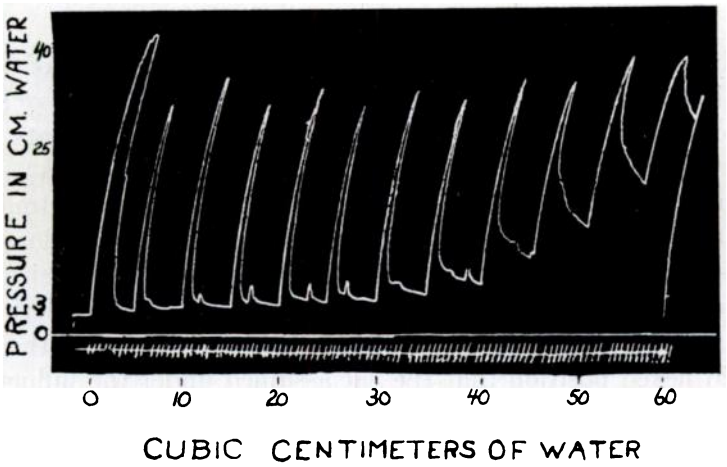

FIG. 4. NEMBUTAL ANESTHESIA 29 MGM. PER KILOGRAM

Initial pressure 2.8 cm. Step-like ascent on filling with passive overflow of urine at 40 cm. of water. No active contraction. Time recorded at 5-second intervals.

occur when more than 33 mgm. per kilogram had been given. However in 9 instances with dosages between 19 and 25 mgm. per kilogram no contraction took place. Other factors besides the dosage per kilogram such as tolerance to the drug, the site of injection, and general condition of the animal must be considered in deciding the extent of depression of vesical activity that the drug will produce.

In general the barbiturates produce a picture of vesical filling not unlike that occurring under ether anesthesia. The initial pressure is low and the resting levels remain steady with these

drugs, which are maintained at a fairly constant concentration in the tissues in contradistinction to the rise or fall which follows slight changes in the depth of ether anesthesia. The bladder fails to adapt to increasing volumes with low pressures as filling nears completion. The terminal passive rise in pressure without active vesical contraction and the presence of residual urine is as constant with deep barbiturate anesthesia as with ether. When the pressure reaches a certain height a small amount of fluid is passively forced out through the urethra.

4. Bladder readings under bulbocapnine

In attempting to reproduce in animals the picture of vesical activity such as Tauber, Lewis and Langworthy (4) have shown in catatonic patients, some readings were made with cats under the influence of bulbocapnine phosphoricum (Merck). This is a drug of the apomorphine series, producing a catatonic-like picture in animals and man when given in adequate doses. It was apparent that the drug did not paralyse active vesical contraction as ether, nembutal and dial do, although rendering the animal sufficiently quiet to allow catheterisation. In the usual rigid flexed position that the cat assumed under the influence of bulbocapnine, catheterization was often difficult as the instrument did not pass freely into the bladder. The average dosage utilized was 30 grams per kilogram with a minimum of 17.6 mgm. and a maximum of 37 mgm. According to Schaltenbrand (5) catalepsy occurs with doses between 10 and 25 mgm. per kilogram.

The following record (fig. 5) was obtained after the subcutaneous injection of 29 mgm. per kilogram of this drug. There was difficulty catheterizing the animal; the initial pressure was 4.2 cm. Filling occurred with a slow rise of pressure to 11 cm. after the fifteenth 5-cc. increment was added. Following the succeeding addition of 5-cc. there was a forceful contraction of the bladder and complete emptying took place. No residual urine was left in the organ.

Certain variations are evident in bladder filling with the use of this drug as contrasted with ether or the barbiturates. First,

the initial resting vesical pressure was high. This was true in all 17 observations and varied from 0.5 to 5 cm. greater than the usual initial pressure under nembutal anesthesia. Furthermore nine of the records were obtained after abdominal wall denervation. Following this procedure the tense flexed body posture was not adopted, showing that this position with its possible increase in intra-abdominal pressure had little to do with the initial increase in vesical tonus. In two animals studied under bulbocapnine both previous to and following denervation

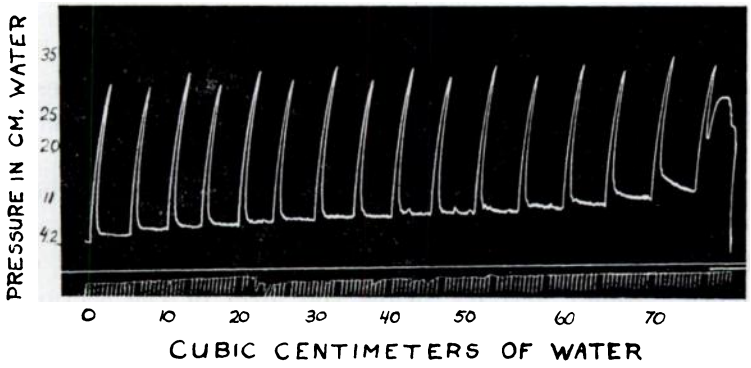

FIG. 5. BULBOCAPNINE ANESTHESIA 29 MGM. PER KILOGRAM

Initial pressure 4.2 cm. water. Filling shown with slow rise in pressure to 11 cm. of water. Note sharp spontaneous vesical wave reaching 30 cm. of water with complete emptying of the bladder. Time recorded at 5-second intervals.

of the abdominal wall there was no significant change in the initial pressure.

Second, filling occurred exactly as in the unanesthetised animal (fig. 1). The bladder adapted immediately to the increased volume and throughout the period of filling maintained almost a constant level of pressure. Thus the pressure increased from 4.2 to 9.0 cm. while adding 70-cc. Third, after reaching a resting level of 11 cm. the succeeding stretch led to a fused vesical contraction. This was powerful and was maintained until emptying was complete, so that no residual urine was left in the bladder.

In every point except the initial high intravesical pressure the bladder activity corresponded to that in the unanesthetized cats. It differed from filling under ether and barbiturate anes-

thesia as fluid was held at a higher initial pressure than with the latter drugs. Also at the end of filling with nembutal or ether (figs. 2 and 4) the pressures ascended rapidly, suggesting the muscle was no longer adapting to changes in volume, there was no active detrusor contraction, and residual urine was regularly observed.

5. Further studies on the action of bulbocapnine on the bladder

To determine whether the effect of the drug was expressed through the functional activity of a particular portion of the nervous system five animals were studied before and after spinal cord transections and three others were examined following anterior sacral root resection, posterior sacral root resection and resection of both the sacral spinal cord and abdominal sympathetic chains.

Two of the readings following transection of the spinal cord at the level of the tenth thoracic segment were made on the fifth post operative day, one on the fourth, and the last on the eleventh. Reflex activity below the level of the section was present in all cases at these periods as manifested by presence of tendon jerks and flexor movements in the hind legs. This was most marked in the cat which was studied after 11 days.

In the animal studied on the fourth day post-operatively the few spontaneous vesical waves were abolished for 4 minutes after subcutaneous injection of the drug. Then small rapid waves, five to six per minute, were seen for another 4 minutes and finally larger, more powerful fluctuations became established at a rate of 3 per minute. A similar picture occurred in one of the 5-day experiments with an increase in frequency and amplitude of the spontaneous waves appearing seven and one-half minutes after the injection of the drug. Fifteen minutes following the injection the rate had decreased to 3 waves per minute while the amplitude still remained great varying from 6 to 22 cm. and associated with passage of urine when the intravesical pressure surpassed 17 cm. of water. The third animal showed only depression of the normal but slightly established rhythmic vesical activity.

The record of the eleven day experiment showed that three minutes after injection of 29 mgm. per kilogram of the drug the base line of pressure rose steeply from 14 to 24 cm. where it remained. Peak like waves occurred about once each minute with expulsion of urine. The sudden increase in tone with the large waves suggest the drug was very rapidly absorbed.

The pattern of vesical activity following posterior root section when the cat was under bulbocapnine anesthesia was essentially that seen a few days after spinal cord transection. The few waves present in the preanesthetic record were first obliterated, then increased in rate and later the previous rhythm returned. The resting pressures were much higher than in the unanesthetized animal at the same point in the curve.

The only record of resting intravesical pressure obtained after anterior root section showed a steady rise from 5.5-cc. to 16 cm. of water over 21 minutes. The filling curves were modified greatly. Without anesthesia the organ held 130-cc. with a few active spurts of urine when the resting pressure equaled 16 cm. Following bulbocapnine the pressure reached 16 cm. when only 50-cc. had been added. No further fluid could enter even under a hydrostatic pressure of 60 cm. of water. No urine was forced about the catheter. In one instance on the fourth post operative day the drug showed no effect on bladder tone or reaction to filling when the organ was completely isolated from the spinal cord by transecting the abdominal sympathetic chains and the anterior and posterior sacral roots.

DISCUSSION

The work reported here attempts to determine the influence of certain anesthetics and hypnotics on vesical activity and micturition. In the past the use of these drugs has complicated the interpretations of the experimental data, and at present their utilization offers an obstacle to further detailed examination of the nervous control of micturition.

Barrington first pointed out that the fusion of the vesical waves into a single strong and continued contraction which effects complete bladder emptying is dependent on the integrity of

long reflex arcs extending to the region of the midbrain. He stated that complete micturition never occurs under the influence of chloroform or deep ether anesthesia. Langworthy and Kolb later substantiated the suprasegmental control and showed further that it is released after extirpation of the motor cortex in the cat. Since then Langworthy et al. (3) have obtained characteristic records showing hyperactive reactions to sudden stretch in unanesthetized patients suffering from injury to the cortical projection paths.

Langworthy and Hesser (6) stated that they were unable to demonstrate the increased response to stretch in decorticate cats and suggested that it might in part be due to the anesthetic (nembutal) or to the fact that stretch responses are not released as effectively after cortical injuries in cats as they are in man. We have prepared cystometric records of three decorticate cats previous to and following the use of the various drugs mentioned here but have never demonstrated such stretch waves, suggesting that the hyperactive responses are not as effectively released in the cat as in man. But the suppressing effect which ether and nembutal have on micturition in the normal cat leads us to assume that such reactions would be inhibited in man or in monkeys in cases where these excessive reactions are expected to occur. Such studies should be made under bulbocapnine or in the unanesthetized preparation.

Quigley, Barlow and Himmelsbach (7) have demonstrated the depressant effect of nembutal on motility and tone in the intestinal tract while Gruber (8) has shown that in the intact unanesthetized dog the barbiturates produce depression of intestinal peristalsis which endures longer when the organ is distended strongly. It is recognized that ether effects muscle as well as nerve. It might be assumed from these facts alone that the integrated actions of micturition depending on long spinal reflex pathways would be adversely influenced by these drugs. The facts presented above support such a belief. These observations suggest a basis for post-operative retention. Its treatment with acetyl choline derivatives is rational as Levin (9) has shown micturition will take place in an animal heavily

narcotized with nembutal following the subcutaneous injection of acetyl-B-methyl choline.

Bulbocapnine has long been known to have an effect on autonomic function. Salivation, vomiting, defecation and urination resulting from its administration have been mentioned but have never been studied in any detail. In recent years the peculiar "cataleptic" condition induced by the drug and its effects on tone have led to a considerable discussion as to whether the drug acted specifically on some particular portion of the nervous system or had a more diffuse effect (2). Most of the experimental studies which have been made were concerned with tone in skeletal muscles following ablation of various portions of the nervous system. Recently Ward and Kolb (10) have shown that while the action of the drug is diffuse as regards the central nervous system, the peripheral reflex arc, must be intact in order for it to express its action locally. The drug has no effect on muscle alone in the production of increased tone as Ferraro and Barrera (11) suggest.

The degree of increased vesical tone and effectiveness of micturition depend on what reflex pathways concerned with micturition are still intact. In the normal animal following bulbocapnine administration the bladder is forcefully and completely emptied. After the return of reflex activity in the spinal cat the injections of the drug cause first an abolition or decrease in the vesical waves lasting about four minutes. This may be associated with the pain due to the injection. The waves then reappear being more rapid but gradually increasing in amplitude to become several times the original size. The unusual and sudden increase in tone and the high pressure waves occurring within three minutes of injection in the eleven day survival may have been due to sudden release of the drug into the blood stream.

In these animals micturition was never complete and consisted only in spurts of urine. This supports the contention that the fused wave of vesical activity resulting in complete bladder emptying is dependent on higher reflex pathways. After section of the posterior sacral roots or anterior sacral roots with the sympathetic chain intact the drug still effected a rise in intra-

vesical pressure but no change in the few waves which were present. With division of both sympathetic and parasympathetic nerves and consequent isolation of the bladder the drug had no effect on vesical response to filling. These observations, though too few, suggest that as with skeletal muscle, the presence of connections with the central nervous system are necessary in order that the autonomic effects of bulbocapnine may be expressed.

Bulbocapnine is the only drug of the series examined which may be utilized in studying the nervous control of micturition without seriously modifying reflex activity.

SUMMARY

1. One hundred and sixteen kymographic records of vesical filling were analyzed in relation to the changes produced by the type of anesthetic used. The records were obtained from thirty-four normal animals, five spinal animals, three decorticate cats and four others with various lesions of the sacral roots, and sympathetic chain.

2. Nembutal, given in the average dose of thirty mgm. per kilogram, depresses stretch responses and prevents a sustained vesical contraction when vesical filling is complete. Residual urine is always present in the bladder even though some emptying may occur.

3. Ether likewise depresses stretch responses and active vesical contraction, and causes the presence of residual urine. On increasing the depth of anesthesia, the resting vesical pressure rises.

4. Bulbocapnine phosphoricum (Merck) renders the animals immobile and heightens parasympathetic activity. It increases the initial resting pressure although filling occurs normally. Stretch responses are obtained and the final contraction is forceful and maintained so that no residual urine occurs.

5. The increased intravesical pressure produced by this drug is not related to the rigidity of the abdominal wall. It is noted in spinal animals and after removal of the sacral cord and sympathetic chain.

6. Bulbocapnine is the most suitable of the drugs examined for use in the study of the nervous control of micturition.

We wish to express our thanks to the Merck Company who very kindly supplied the Bulbocapnine used here.

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