LIST OF PROCEDURES DONE

PROJECT REPORT

TITLE OF THE PROJECT: **INTRA-ARTERIAL v/s INTRA-VENOUS MANNITOL TO CONTROL EXPERIMENTALLY INDUCED RAISED INTRACRANIAL PRESSURE IN A CANINE MODEL**

NAME....Dr. AADIL.S.CHAGLA

PROGRAMME : MCh. NEUROSURGERY

MONTH & YEAR OF SUBMISSION : December, 1991

CERTIFICATE

I, Dr.......AADIL.S.CHAGLA...........................hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Signature..............................

Place :
Trivandrum

Name in Dr. AADIL.S.CHAGLA...............
capital letters

Date :
December, '91

Forwarded. He has carried out the minimum requirement of procedures / etc.

4/12/91

Signature
Head of the department
(Prof. D.ROUT)

INTRODUCTION AND AIM

The management of patients with raised intracranial ressure (ICP) continues to pose a stiff challenge to the eurosurgeon and raised ICP still remains a common cause of death n neurosurgical practice. In the earlier days, emphasis was laid n the clinical diagnosis of increased ICP and methods of reatment evolved, as experience with intracranial lesions and heir surgical therapy increased. Over the past 30 years, ntensive research into the patho-physiology of raised ICP and ts effects on brain function, metabolism, blood flow, and other arameters has been undertaken. The introduction of modern echniques for monitoring ICP has provided a firmer basis for he diagnosis and treatment of raised ICP.

Lundberg,[11] in 1960, was the first to continuously measure CP using a cannula in the frontal horn of the lateral ventricle hrough a burrhole. Prior to this time, ICP was measured only nfrequently and usually indirectly via lumbar puncture. undberg's series was followed by a variety of laboratory nvestigations of a variety of experimentally induced raised ICP nd its clinico-pathological effects and management.

The present experiment is aimed to study the effect of intra-arterial mannitol as compared to intra-venous mannitol in the control of experimentally induced raised ICP in a canine model.

MATERIALS AND METHODS

EXPERIMENTAL ANIMAL:

This study was carried out on six healthy mongrel male dogs weighing between 13.5 to 14.5 Kgs.

PREPARATION OF THE ANIMAL :

The dogs were dewormed and inoculated against rabies, canine hepatitis, leptospirosis and distemper over three to four weeks.

ANESTHESIA:

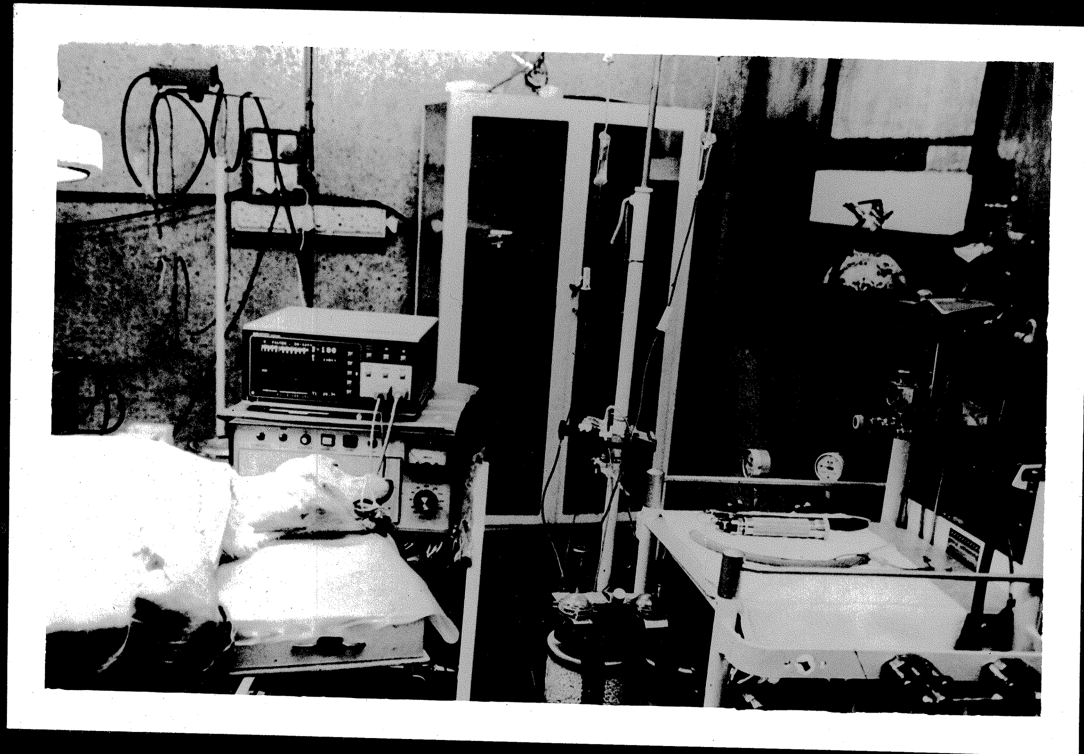
Premedication (calmpose and atropine) was administered half an hour before induction of anesthesia.

General anesthesia was induced using thiopentone (25mg/Kg body wt.) The dogs were intubated with cuffed endo-tracheal tubes using "crash intubation" technique and put on controlled ventilation, maintained on O_2:N_2O in the ratio 3:2 with intermittent doses of gallamine (2.5mg/Kg body wt.).

ECG leads were connected (three lead system) and the urinary bladder was catheterized.

PROCEDURE:

With the animal under G.A., placed in (L) lateral position with the neck extended ; the neck and head were shaved, prepared and draped.



OPERATION THEATRE SET-UP

RADIOMETER BGA 3

for blood gas analysis

muscle was sutured around the tube over the dura. The wound was closed in layers with a water-tight closure of temporalis muscle and fascia. The ventricular cannula was connected to the transducer (Hewlett Packard system) to record the ICP.

Repeated blood gas analyses were carried out to ensure that adequate ventilation was being administered and pH was being maintained.

ICP was experimentally elevated by producing hypercarbia which was attained by giving CO_2 (200-500ml/liter). Blood gas analysis was repeated to verify the rise in pCO_2. After the elevated ICP stabilised, the animal was injected with 20% mannitol (1g/Kg body wt.) -- intra-arterial mannitol, equally divided into both the common carotids, in three dogs ; and -- intra-venous mannitol into the internal jugular in the remainder, for comparison. The arterial blood gases and blood pressure along with the ICP, CVP and Urine output were repeatedly monitored over the next one and a half to two hours and the results noted.

OBSERVATIONS AND RESULTS

After overcoming the initial technical difficulties, in which dog-1 did not withstand the procedure and suffered a cardiac arrest while hypercarbia was being induced ; and dog-3 developed profuse peri-tubal csf leak not permiting a proper measurement of ICP (thus, could not be included in the study) ; dogs-2, 4, 5 & 6 were successfully studied on ; with two intra-arterial bilateral carotid injections (dogs-2 & 6) and two intra-venous jugular injections (dogs-4 & 5). The study was limited by the restricted number of dogs for the experiment.

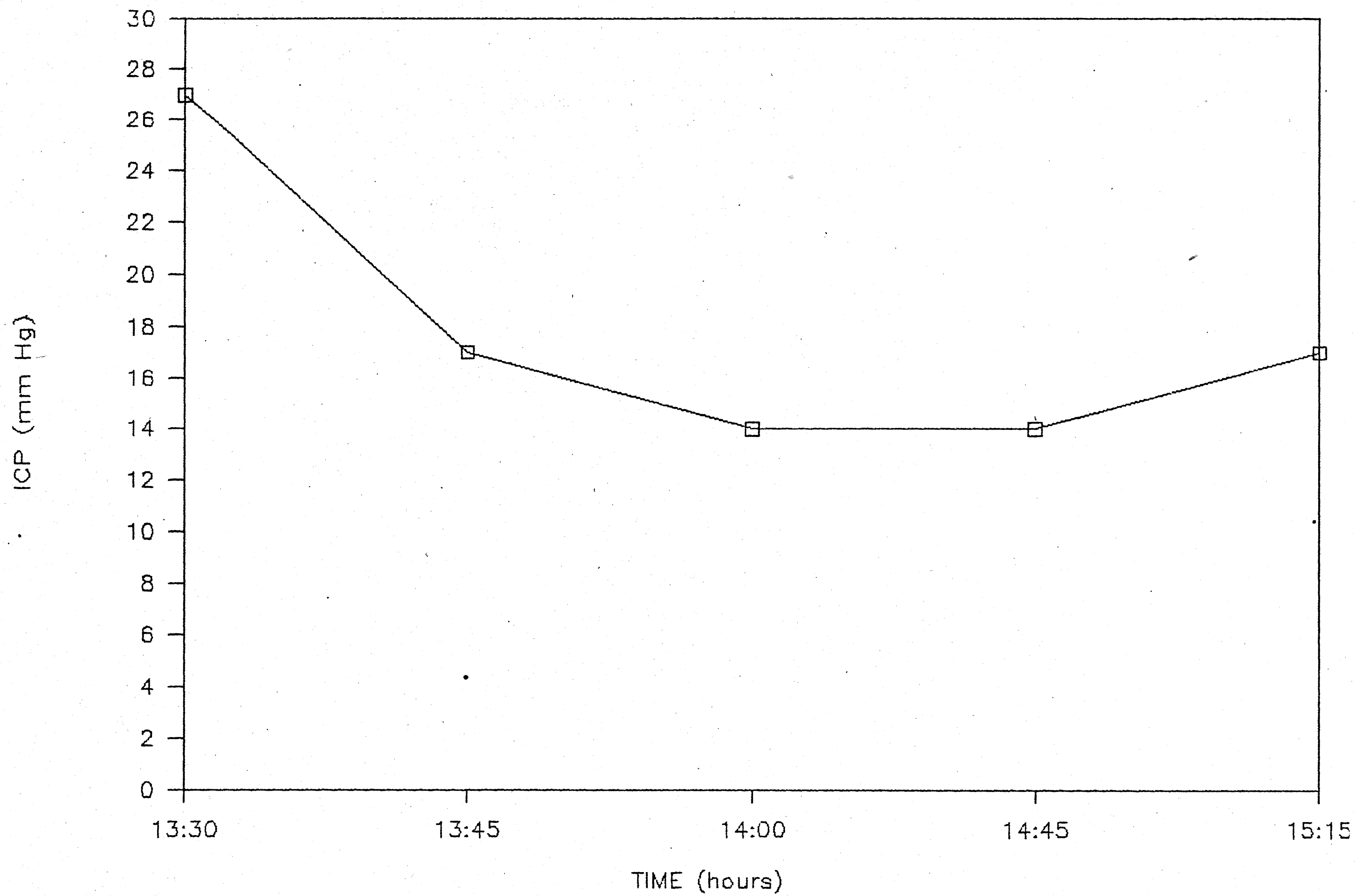
The observations are tabulated, as follows :

A-ARTERIAL MANNITOL --->

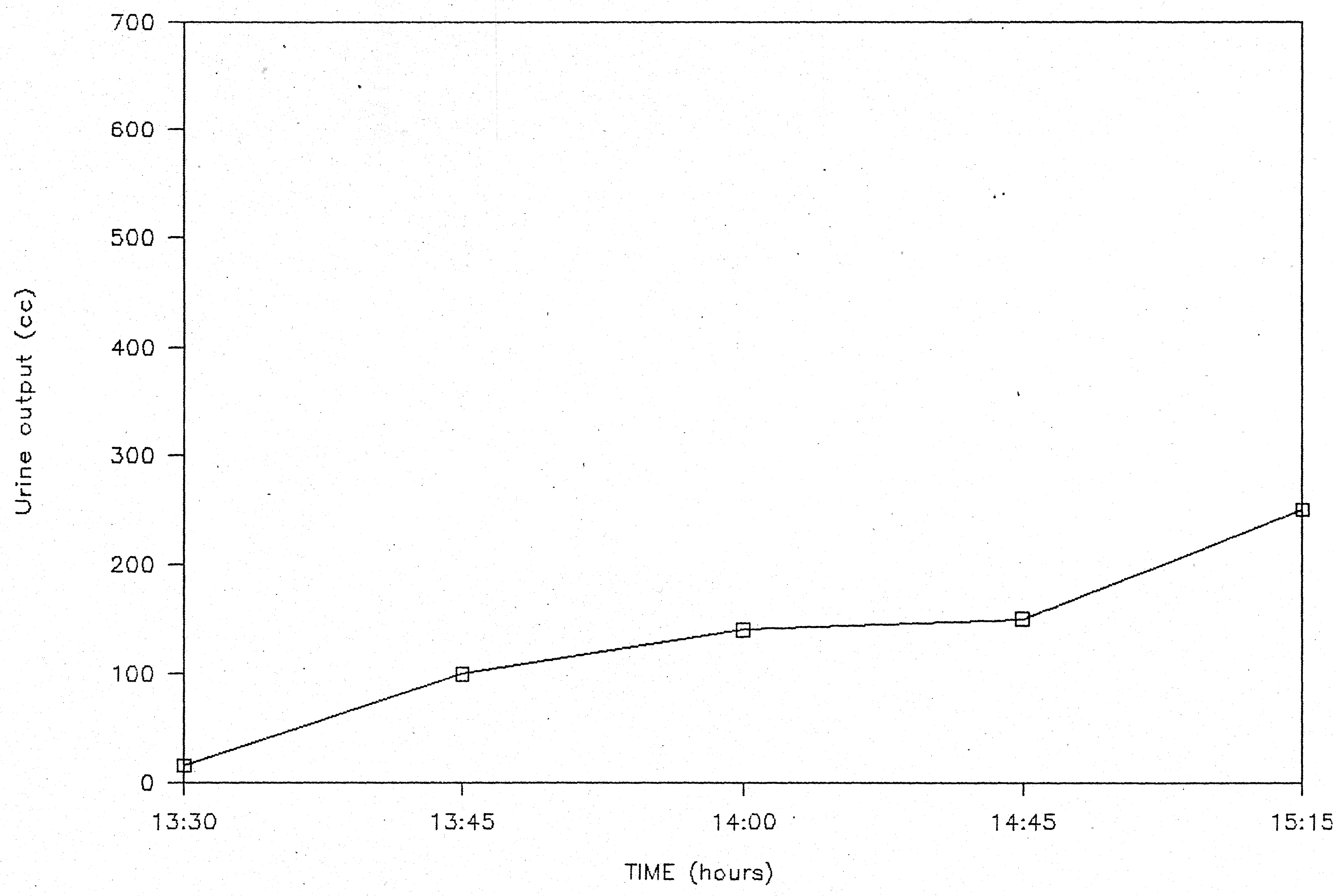
DOG-2

TIME hours	ICP mm Hg	pCO2 mm Hg	pO2 mm Hg	pH	CVP cm	BP(sys) mm Hg	BP(dia) mm Hg	Urine out out cc
11:30		34.30	255.00	7.341	6.0	150	120	
12:00	6.0	33.20	234.00	7.352	6.0	130	110	
12:30	10.0	45.70	242.00	7.398	7.0	130	110	
13:00	20.0	51.70	327.00	7.263	8.0	150	120	
13:30	27.0	51.70	357.00	7.278	6.0	140	110	10
13:45	17.0	77.80	297.00	7.198	4.0	120	92	15
14:00	14.0	73.40	273.00	7.251	4.0	120	96	100
14:45	14.0	36.70	278.00	7.365	4.0	120	96	140
15:15	17.0	36.10	284.00	7.446	6.0	120	90	150
								250

DOG-2


ICP (mm Hg)
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
13:30
13:45
14:00
14:45
15:15
TIME (hours)

DOG-2



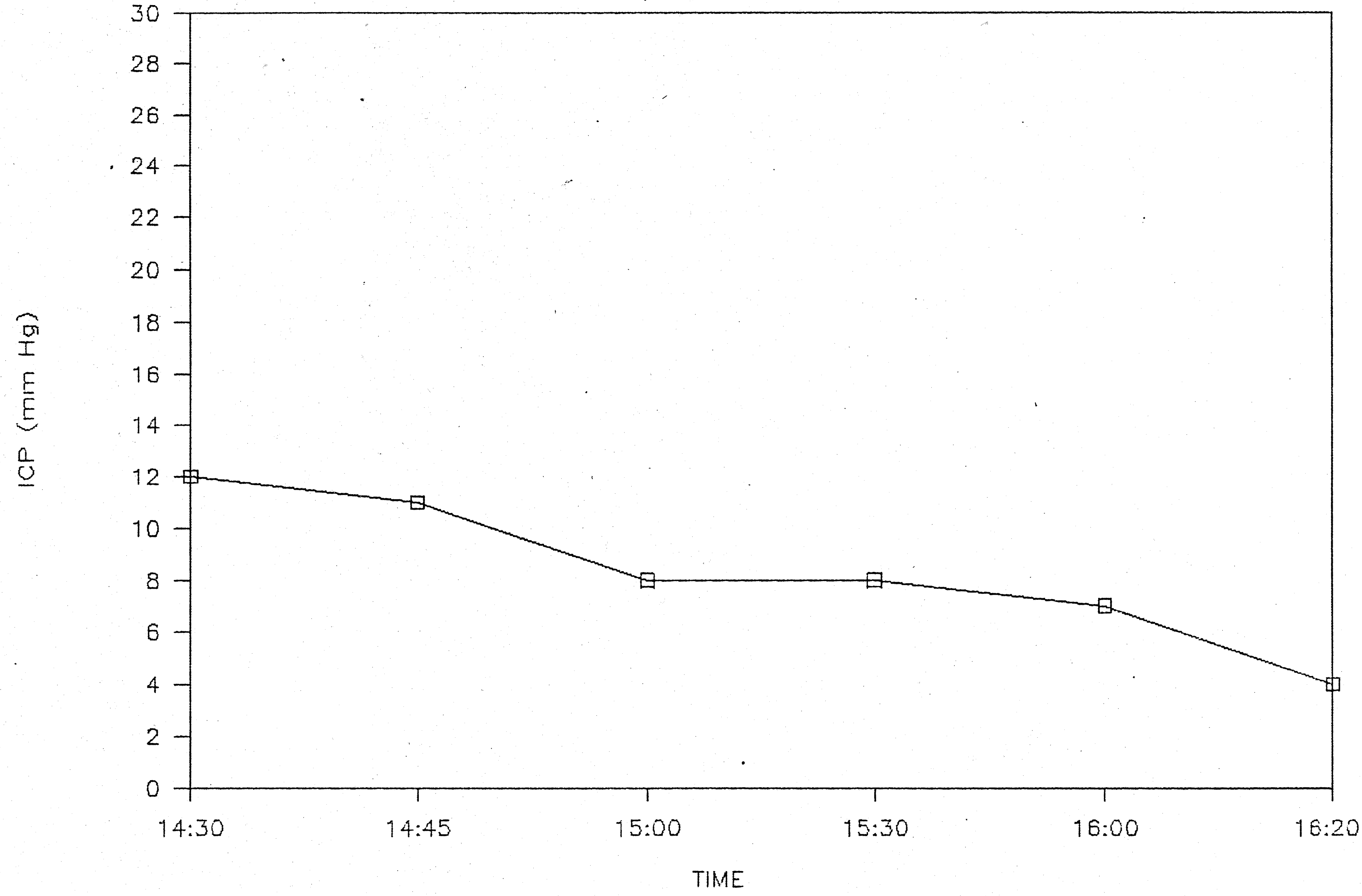
700
600
500
400
300
200
100
0
Urine output (cc)
13:30
13:45
14:00
14:45
15:15
TIME (hours)

TRA-VENOUS MANNITOL --->

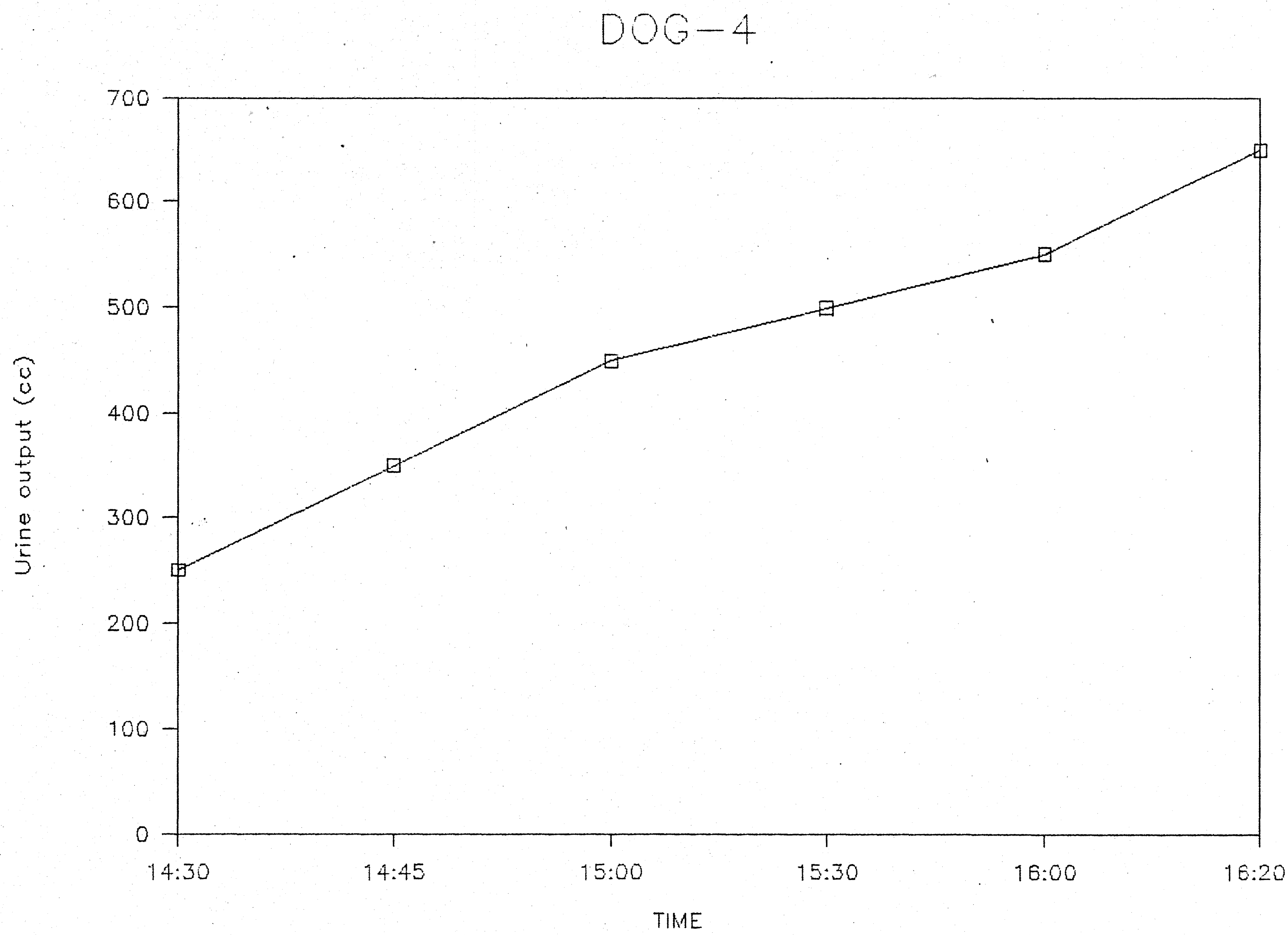
DOG-4

TIME hours	ICP mm Hg	pCO2 mm Hg	pO2 mm Hg	pH	CVP cm	BP(sys) mm Hg.	BP(dia) mm Hg	Urine out put cc
11:00		26.00	214.00	7.455	2.0			
11:45		34.10	291.00	7.435	2.0			
12:00	7.0	36.50	316.00	7.426	2.0			
13:00	7.0	96.10	318.00			112	90	
14:30	12.0	77.20	283.00	7.184	1.5	112	90	250
14:45	11.0	69.80	298.00	7.217	0.5	116	96	350
15:00	8.0	67.50	312.00	7.238	1.5	110	91	450
15:30	8.0	76.80	300.00	7.168	1.5	110	90	500
16:00	7.0	79.30	308.00	7.245		117	99	550
16:20	4.0	60.90	317.00	7.233	1.0	117	99	650

DOG-4



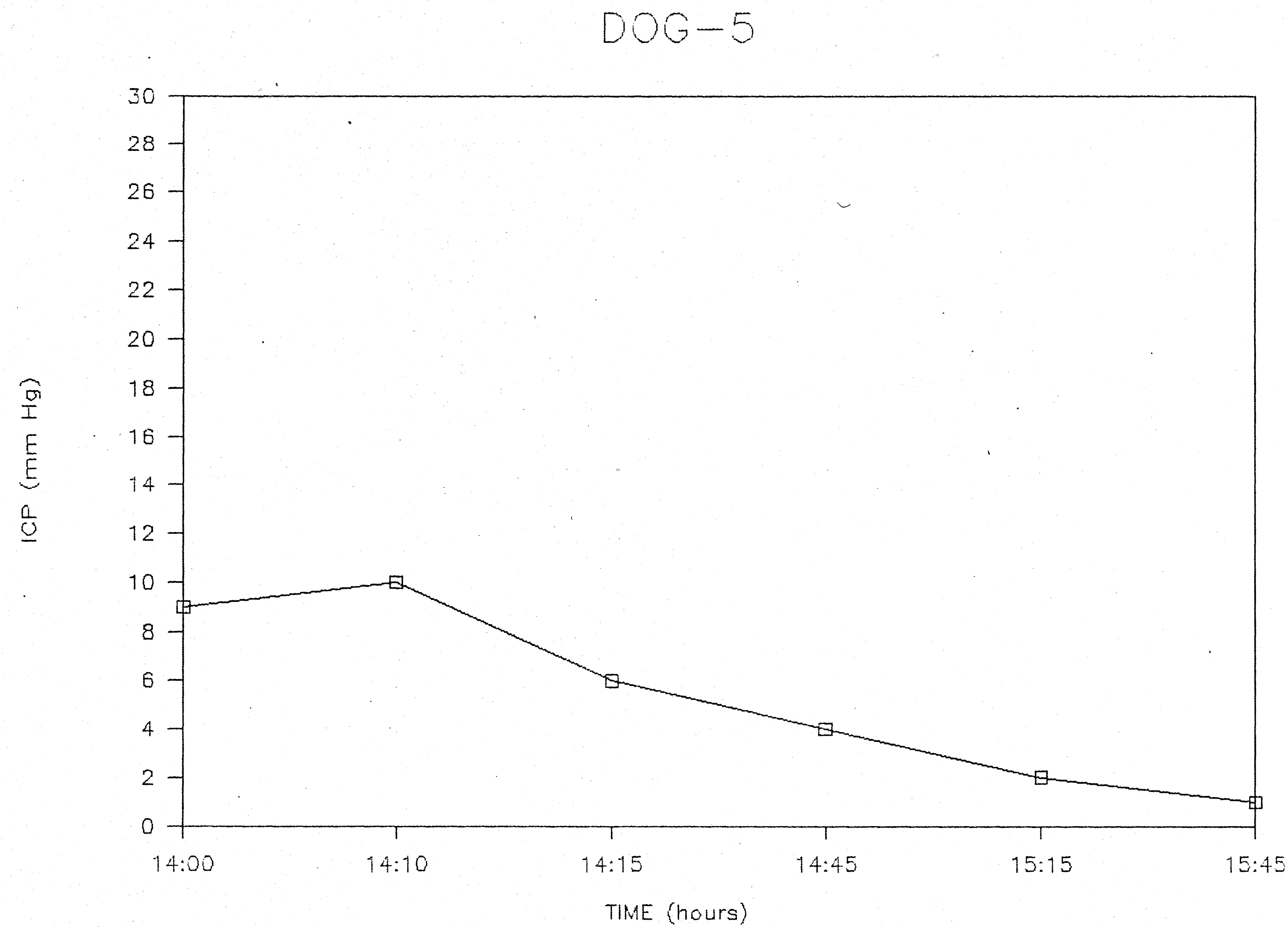
ICP (mm Hg)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
14:30
14:45
15:00
15:30
16:00
16:20
TIME

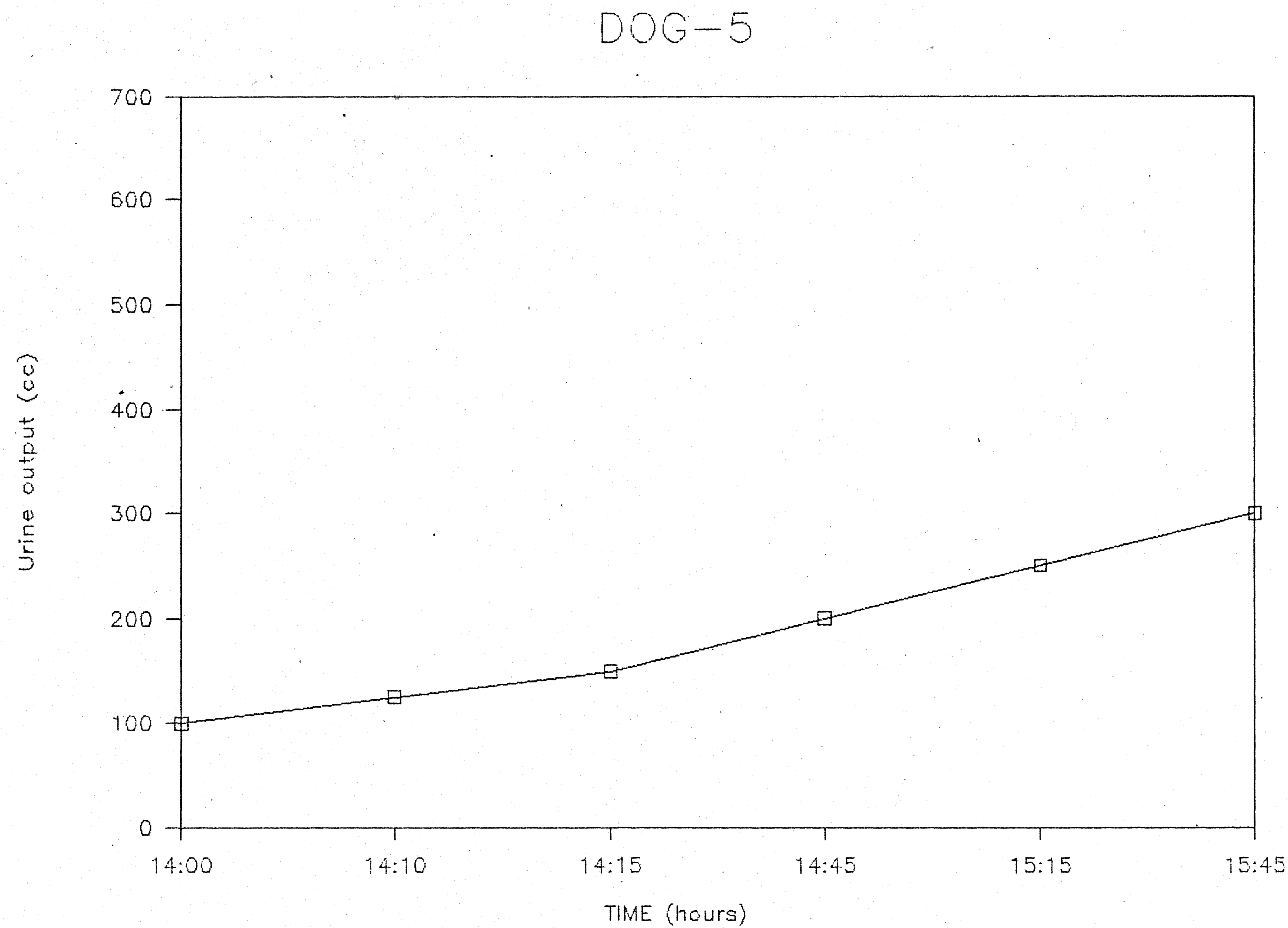

DOG—4
Urine output (cc)
700
600
500
400
300
200
100
0
14:30
14:45
15:00
15:30
16:00
16:20
TIME

NTRA-VENOUS MANNITOL --->

DOG-5

TIME hours	ICP mm Hg	pCO2 mm Hg	pO2 mm Hg	pH	CVP cm	BP(sys) mm Hg	BP(dia) mm Hg	Urine out put cc
12:00		31.20	282.00	7.383	3.5	140	110	
12:40	6.0	31.60	352.00	7.372	4.5	140	109	
13:15	12.0	80.60	333.00	7.097	5.0	130	104	50
14:00	9.0	75.80			5.0	130	106	100
14:10	10.0				4.5	138	117	125
14:15	6.0	79.90	250.00	7.142	4.5	128	109	150
14:45	4.0	84.80	326.00	7.121	3.5	130	110	200
15:15	2.0	53.80	316.00	7.338	2.0	130	120	250
15:45	1.0	40.20	307.00	7.375	2.0	130	120	300


DOG—5
ICP (mm Hg)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
14:00
14:10
14:15
14:45
15:15
15:45
TIME (hours)

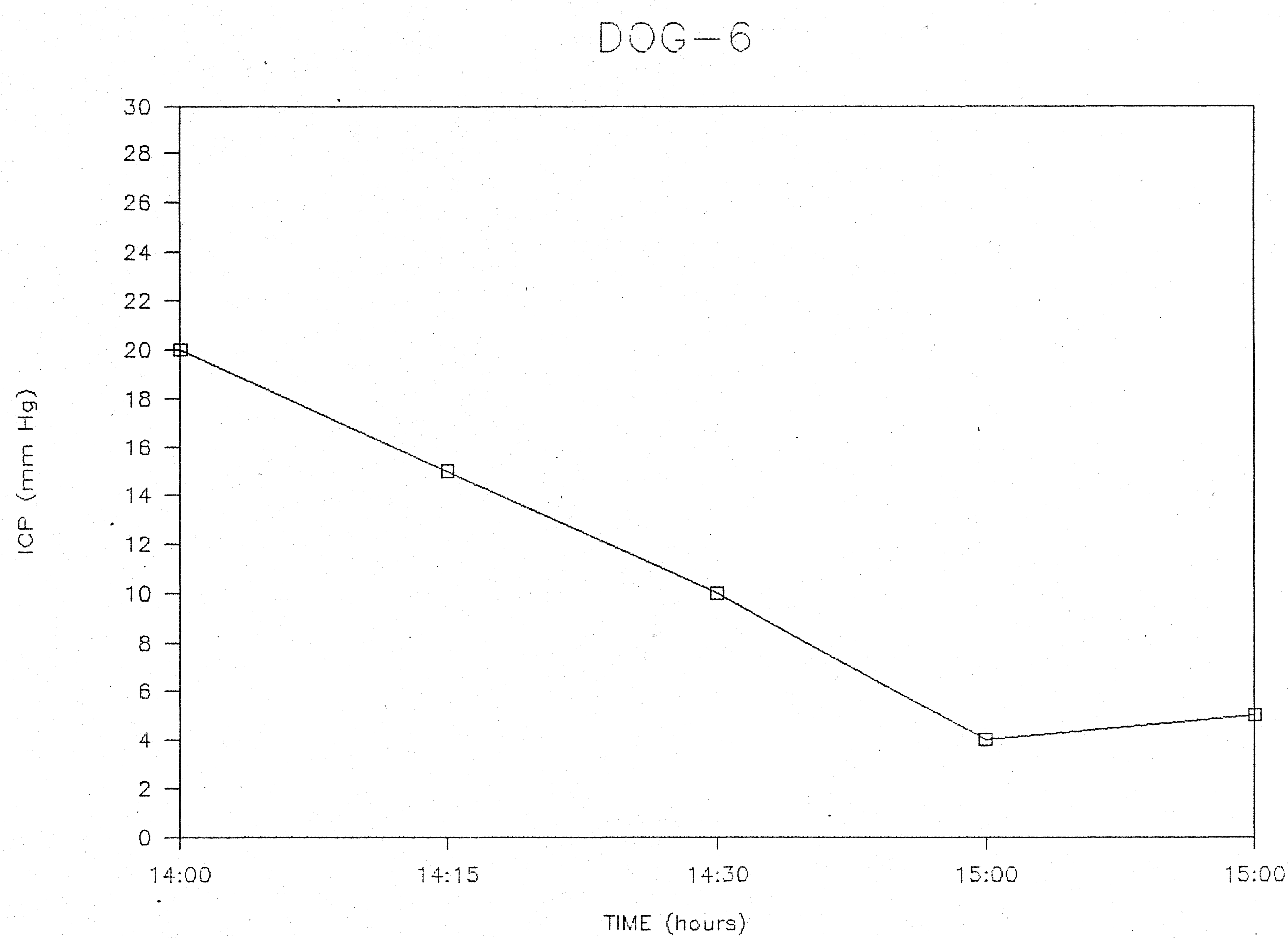


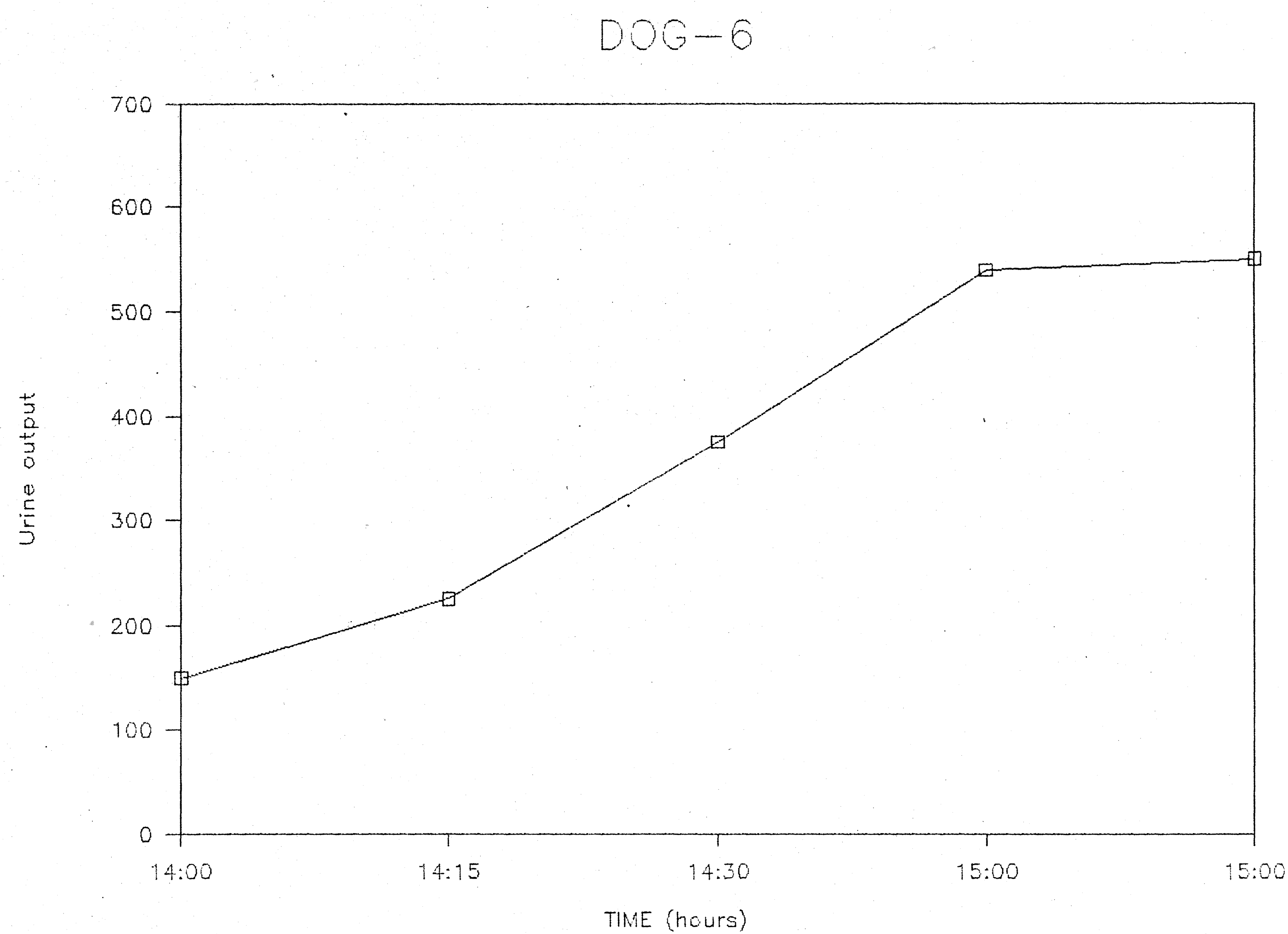
DOG-5
Urine output (cc)
700
600
500
400
300
200
100
0
14:00
14:10
14:15
14:45
15:15
15:45
TIME (hours)

INTRA-ARTERIAL MANNITOL --->

DOG-6

TIME hours	ICP mm Hg	pCO2 mm Hg	pO2 mm Hg	pH	CVP cm	BP(sys) mm Hg	BP(dia) mm Hg	Urine out out cc
11:45		29.60	266.00	7.534	8.0	101	91	
12:15	7.0	34.70	245.00	7.520	10.0	102	91	50
13:30	25.0	64.30	212.00	7.375	10.0	102	91	150
14:00	20.0	68.90	258.00	7.426	10.0	102	92	150
14:15	15.0				7.0	80	74	225
14:30	10.0	74.40	253.00	7.180	6.0	97	90	375
15:00	4.0	68.00	321.00	7.195	6.0	102	92	540
15:00	5.0	53.30	135.00	7.322	6.0	101	91	550


DOG-6
ICP (mm Hg)
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
14:00
14:15
14:30
15:00
15:00
TIME (hours)


DOG—6
Urine output
700
600
500
400
300
200
100
0
14:00
14:15
14:30
15:00
15:00
TIME (hours)

DISCUSSION

In 1962, Wise and Charter[19] reported the use of mannitol to treat raised ICP. Mannitol is not metabolised and has a restricted access across the blood brain barrier. Thus, in the presence of an intact blood brain barrier, an osmotic gradient is set up and water is driven from the brain to the plasma. When 1gm/Kg body weight of mannitol is given over a period of 10 minutes; a rise in serum osmolality of approximately 20 to 30 m.osmol/litre occurs, with return to control levels in about 3 hours.[17] Studies show a mean intracranial pressure reduction of 52% after injection of the above mentioned dose; the maximal pressure reduction was obtained at an average of 90 minutes post injection; the ICP returned to control levels after 4 hours post injection.[6]

Marshall et al.[12] showed that reduction of ICP with a dose of 0.25gm/Kg was equal to the response obtained with 0.5gm to 1gm/Kg; considerable reduction in ICP occured with increase in osmolality of as little as 10 m.osmols/litre. The smallest possible effective dose has been advocated to guard against a possibility of a "rebound" phenomenon and severe hyperosmolality produces renal damage. Miller and Leech[10,14] showed that mannitol improved the compliance of the brain to a greater degree than its mere beneficial effect on ICP, thereby favourably influencing the slope of the volume / pressure relationship. Also, mannitol has the ability to decrease csf production which also contributes to lowering ICP. Mannitol increases cerebral blood flow and cerebral oxygen consumption in patients independently of its effect on ICP.[1,7] With rapid intra-venous infusion of a large dose of mannitol, plasma volume increases more rapidly than renal clearance of additional fluid and a transient increase in cerebral blood volume and ICP is observed.[3]

In this study, intra-arterial injection of mannitol produced an immediate fall in ICP with no initial rise in ICP as seen with the intra-venous administration (dog-2 : a fall of 10mm Hg and dog-6 : a fall of 5mm Hg : within 5 minutes after injection). The effect is extremely rapid with the intra-arterial injection which commences even before the completion of the bolus injection of mannitol, which is given over a period of 10 minutes. The fall in ICP continued for about one hour after which its effect seemed to have weaned off, with a small rise in ICP, noted in both the dogs studied. The drop in ICP was noted even before the urine output began to increase which is also worth mentioniong. Following intra-arterial injection there was a fall in BP with a corresponding fall in CVP which either returned to its original level or continued to remain low, but stabilized.

As compared to the above, the intra-venous bolus produced a rise in ICP (seen in dog-5) and took nearly 15 minutes after the commencement of the mannitol dose to produce a fall in ICP which continued to fall with a maximum effect being reached at about one and a half hours. Similar observations were made by others.[3,6] There was a definite rise in BP, (as seen in both the dogs-4 & 5) and CVP remained nearly static initially (as seen in dog-5) or showed an initial fall which stabilized (as seen in dog-4). The increased urine output corresponded to the fall in ICP, unlike the arterial injection where the fall in ICP occured before the diuretic action.

The study has been handicapped mainly by the limited availability of dogs for the experiment. Though it is stated that to tap the lateral ventricle of the dog is rather difficult, the same was achieved in all the dogs studied. It was unfortunate that the first dog developed cardiac arrest while producing hypercarbia, and the third dog studied had a significant peri-tubal leak not permitting a proper ICP recording. The remaining four dogs produced a successful study and the dogs tolerated the procedure well. The main problem faced in the experiment was to prevent csf leak from the puncture site and in order to achieve the same, the following points were important.

1. A good orientation of the lie of the ventricle, for proper placement of the catheter and avoiding repeated taps. This was obtained by studying the anatomy of the dog ventricle;[5,13] and a ventriculogram using per-operative C-arm facilities under fluroscopic control; as was done in the first experiment. The ventricle was hit at first attempt in all the dogs, except dog-3 in which an accurate ICP recording could not be obtained and the dog was excluded from the study.

2. A small puncture hole in the dura was made, rather than a cruxiate incision with coagulation of its margins. Haemostasis was achieved using pressure with moist cotton pledgets and saline irrigation, rather than cautery. (Only monopolar cautery was available.)

3. In case of a small peri-tubal leak, a stitch was taken through the dura and a muscle patch was grafted at the site.

4. The parietal wound was closed in layers with particular attention to the temporalis muscle and fascia.

5. Sealing the puncture site with cyano-acrylate[18] could not be achieved due to non-availability of the same. This method would probably have been the easiest and surest way of preventing peri-tubal csf leak.

On analysis of the results, it appears that intra-arterial dministration of mannitol has the following advantages over ntra-venous administration :

. No initial rise in ICP.

. Extremely rapid action with a marked fall in ICP.

. The instantaneous fall in ICP appears independent of its iuretic action.

. No initial rise in BP.

The most likely explanation for the above facts is that ntra-arterial mannitol produces an immediate rise in serum smolality within the intracranial vessels, creating an osmotic radient which causes a shift of water from the brain to the lasma, producing a marked fall in ICP. There is a fall in BP, econdary to the fall in ICP. Besides the benefits just entioned, which may prove vital in a critically ill patient, ther possible benefits may also be potentiated further by intra-rterial administration.

. In cases of supra-tentorial lesions with unilateral causes of aised ICP which may produce uncal and sub-falcine herniations, psilateral administration of intra-arterial mannitol will irect its action at the pathlogical site (and side), rather than he entire brain, reducing the mass effect and correcting the mid-line shift more efficiently. Cushing[4] had stated that the pressure exerted by an intracranial foreign body "is not transmitted equally throughout the cerebral chamber and in consequence the circulatory embarassment in corresponding degree is unevenly felt".[9]

2. Shapiro[16] has morphologically shown that intracranial hypertension produces compression on cerebral blood vessels, reducing cerebral blood flow and perfusion. It is stated that hyperosmolar agents have significant vasodilator properties, increasing capillary diameter and blood volume.[8] Mannitol, also, decreases the blood viscosity.[2] Thus, when administered intra-arterially, the above mentioned actions may be further potentiated improving cerebral perfusion and the clinical status of the patient independent of its action on raised ICP.

3. Smaller doses of mannitol may be required than those described by Marshall et al.,[12] thus reducing the possibilities of "rebound", renal damage, electrolyte imbalance and cardiac decompensation ; all known complications of high dose mannitol therapy.

SUMMARY AND CONCLUSION

1. A Canine model was developed to measure ICP, BP, CVP, Urine output and arterial blood gases, and the effect of intra-arterial mannitol was compared with intra-venous mannitol in lowering experimentally induced raised ICP. Out of the six dogs available for the experiment, four were successfully studied on.

2. The main problem encountered, in a technically difficult procedure, was to prevent peri-tubal csf leak producing falacious ICP recordings.

3. The study showed that intra-arterial mannitol produced a rapid, marked fall in ICP with its effects wearing off after one hour, as compared to the intra-venous study which produced a peak action at about one and a half hours.

4. There was an initial rise in ICP following intra-venous administration of mannitol which was not seen in the intra-arterial study, an extremely important feature, as this rise may prove detrimental in a poorly compromised patient with severely raised ICP.

The increased urine output corresponded to the fall in ICP in
e intra-venous study whereas the fall in ICP occured much
fore the drug produced its diuretic action in the intra-
terial study.

The beneficial effects of intra-arterial mannitol will have
be weighed against the feasibility of its administration,
ch may, in the present clinical set up, only be possible at
e time of angiogram studies - for example in SAH grade III & IV
tients with raised ICP or in cases of severe head trauma where
scans are not available and critically ill patients are
bjected to angiogram studies as in many centres in the country.

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